Searched for:: :All of the words:**author:michael** AND **author:cordingley**

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1. Oral Bioavailability and In Vivo Efficacy of the Helicase-Primase Inhibitor BILS 45 BS against Acyclovir-Resistant Herpes...
Duan, Jianmin / Liuzzi, Michel / Paris, William / Liard, Francine / Browne, Abigail / Dansereau, Nathalie / Simoneau, Bruno / (...) / Cordingley, Michael G., *Antimicrobial Agents and Chemotherapy*, Jun 2003
This study investigated the oral bioavailability and efficacy of BILS 45 BS, a selective herpes simplex virus (HSV) helicase-primase inhibitor, against acyclovir (ACV)-resistant (ACVr) infections mediated by the HSV type 1 (HSV-1) dlsptk and PAAr5...

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2. An NS3 protease inhibitor with antiviral effects in humans infected with hepatitis C virus.
Daniel Lamarre / Paul C Anderson / Murray Bailey / Pierre Beaulieu / Gordon Bolger / Pierre Bonneau / Michael Bös / (...) / Montse Llinàs-Brunet, *Nature*, Nov 2003
Hepatitis C virus (HCV) infection is a serious cause of chronic liver disease worldwide with more than 170 million infected individuals at risk of developing significant morbidity and mortality. Current interferon-based therapies are suboptimal...

MEDLINE/PubMed Citation on PubMed

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3. Role of the ATP-Binding Domain of the Human Papillomavirus Type 11 E1 Helicase in E2-Dependent Binding to the Origin
Titolo, Steve / Pelletier, Alex / SauvÃƒÂ©, FrÃƒÂ©dÃƒÂ©ric / Brault, Karine / Wardrop, Elizabeth / White, Peter W. / Amin, Anthony / (...) / Archambault, Jacques, *Journal of Virology*, Sep 2002
Replication of the genome of human papillomaviruses (HPV) is initiated by the recruitment of the viral E1 helicase to the origin of DNA replication by the viral E2 protein, which binds specifically to the origin. We determined, for HPV type 11...

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☐ **4.** Identification of Domains of the Human Papillomavirus Type 11 E1 Helicase Involved in Oligomerization and Binding to the...
Titolo, Steve / Pelletier, Alex / Pulichino, Anne-Marie / Brault, Karine / Wardrop, Elizabeth / White, Peter W. / Cordingley, Michael G. / Archambault, Jacques, *Journal of Virology*, Sep 2002
The E1 helicase of papillomavirus is required, in addition to host cell DNA replication factors, during the initiation and elongation phases of viral episome replication. During initiation, the viral E2 protein promotes the assembly of enzymatically...

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☐ **5.** Antiviral Activity of a Selective Ribonucleotide Reductase Inhibitor against Acyclovir-Resistant Herpes Simplex Virus Type 1...
Duan, Jianmin / Liuzzi, Michel / Paris, William / Lambert, Michelle / Lawetz, Carol / Moss, Neil / Jaramillo, Jorge / (...) / Cordingley, Michael G., *Antimicrobial Agents and Chemotherapy*, Sep 2002
The present study reports the activity of BILD 1633 SE against acyclovir (ACV)-resistant herpes simplex virus (HSV) infections in athymic nude (nu/nu) mice. BILD 1633 SE is a novel peptidomimetic inhibitor of HSV ribonucleotide reductase (RR). In...

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☐ **6.** Discovery of the first series of inhibitors of human papillomavirus type 11: inhibition of the assembly of the E1-E2-Origin...
Christiane Yoakim / William W Ogilvie / Nathalie Goudreau / Julie Naud / Bruno Haché / Jeff A O'Meara / Michael G Cordingley / (...) / Peter W White, *Bioorg Med Chem Lett*, Aug 2003
We have discovered a series of inhibitors of the assembly of the HPV11 E1-E2-origin DNA complex, which incorporate an indandione fused to a substituted tetrahydrofuran.

MEDLINE/PubMed Citation on PubMed

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☐ **7.** HPMPC therapy of MCMV-induced retinal disease in the SCID mouse measured by electroretinography, a non-invasive technique.
Michel Garneau / Gordon T Bolger / Christiane Bousquet / Philip Kibler / François Tremblay / Michael G Cordingley, *Antiviral Res*, Aug 2003
The purpose of these studies was to investigate the use of non-invasive electroretinography for the evaluation of retinal disease and its treatment in an ocular murine cytomegalovirus (MCMV) disease model. While under anesthesia, 10(2.6)plaque forming...

MEDLINE/PubMed Citation on PubMed

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☐ **8.** Inhibition of human papillomavirus DNA replication by small molecule antagonists of the E1-E2 protein interaction.

Peter W White / Steve Titolo / Karine Brault / Louise Thauvette / Alex Pelletier / Ewald Welchner / Lise Bourgon / (...) / Jacques Archambault, *J Biol Chem*, Jul 2003
Human papillomavirus (HPV) DNA replication is initiated by recruitment of the E1 helicase by the E2 protein to the viral origin. Screening of our corporate compound collection with an assay measuring the cooperative binding of E1 and E2 to the origin...

MEDLINE/PubMed Citation on PubMed

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similar results

☐ **9.** Oral bioavailability and in vivo efficacy of the helicase-primase inhibitor BILS 45 BS against acyclovir-resistant herpes...
Jianmin Duan / Michel Liuzzi / William Paris / Francine Liard / Abigail Browne / Nathalie Dansereau / Bruno Simoneau / (...) / Michael G Cordingley, *Antimicrob Agents Chemother*, Jun 2003
This study investigated the oral bioavailability and efficacy of BILS 45 BS, a selective herpes simplex virus (HSV) helicase-primase inhibitor, against acyclovir (ACV)-resistant (ACV(r)) infections mediated by the HSV type 1 (HSV-1) dlsptk and PAA(r)5...

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☐ **10.** Pulmonary embolism associated with tranexamic acid in severe acquired haemophilia.
Minakshi Taparia / Frank T Cordingley / Michael F Leahy, *Eur J Haematol*, May 2002
Tranexamic acid (an antifibrinolytic agent) is of proven benefit in the treatment of bleeding in patients with congenital and acquired coagulation disorders. We report the case of a patient with an acquired Factor VIII inhibitor, who was on a...

MEDLINE/PubMed Citation on PubMed

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☐ **11.** Herpes simplex virus helicase-primase inhibitors are active in animal models of human disease.
James J Crute / Christine A Grygon / Karl D Hargrave / Bruno Simoneau / Anne-Marie Faucher / Gordon Bolger / Philip Kibler / (...) / Michael G Cordingley, *Nat Med*, Apr 2002
Herpes simplex virus infections are the cause of significant morbidity, and currently used therapeutics are largely based on modified nucleoside analogs that inhibit viral DNA polymerase function. To target this disease in a new way, we have identified...

MEDLINE/PubMed Citation on PubMed

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☐ **12.** Depression of diaphragm contractility by nitrous oxide in humans.
Brigitte Fauroux / Jeremy Cordingley / Nicholas Hart / Annick Clément / John Moxham / Frédéric Lofaso / Michael I Polkey, *Anesth Analg*, Feb 2002
Nitrous oxide is widely used in anesthesia and critical care medicine. The effect of nitrous oxide on diaphragm contractility in humans is unknown. We evaluated the effect of a 50% nitrous oxide-50% oxygen mixture on diaphragm contractility in healthy...

MEDLINE/PubMed Citation on PubMed

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☐ **13.** Laser processing
Lauer, William / Trepagnier, Pierre / Smart, Donald Victor / Cordingley, James / Plotkin, Michael / GSI LUMONICS CORPORATION 22300 HAGGERTY ROAD NORTHVILLE MICHIGAN 48167, *UNITED STATES PATENT AND TRADEMARK OFFICE GRANTED PATENT*, May 2003
The invention provides a system and method for vaporizing a target structure on a substrate. According to the invention, a calculation is performed, as a function of wavelength, of an incident beam energy necessary to deposit unit energy in the target...
Full text available at patent office. For more in-depth searching go to LexisNexis
view all 6 results from Patent Offices
similar results

☐ **14.** Controlling laser polarization
Cordingley, James J. / Smart, Donald V. / Plotkin, Michael / Lauer, William / General Scanning, Inc., *UNITED STATES PATENT AND TRADEMARK OFFICE GRANTED PATENT*, Apr 2002
A laser polarization control apparatus includes a polarization modifying device and a controller. The polarization modifying device receives a laser beam and modifies the polarization of the laser beam. The controller adjusts an input to the...
Full text available at patent office. For more in-depth searching go to LexisNexis
view all 6 results from Patent Offices
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☐ **15.** Laser processing
Lauer, William / Trepagnier, Pierre / Smart, Donald Victor / Cordingley, James / Plotkin, Michael / General Scanning, Inc., *UNITED STATES PATENT AND TRADEMARK OFFICE GRANTED PATENT*, Oct 2001
The invention provides a system and method for vaporizing a target structure on a substrate. According to the invention, a calculation is performed, as a function of wavelength, of an incident beam energy necessary to deposit unit energy in the target...
Full text available at patent office. For more in-depth searching go to LexisNexis
view all 6 results from Patent Offices
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☐ **16.** Controlling laser polarization
Cordingley, James J. / Smart, Donald V. / Plotkin, Michael / Lauer, William / General Scanning, Inc., *UNITED STATES PATENT AND TRADEMARK OFFICE GRANTED PATENT*, Jan 2001
A laser polarization control apparatus includes a polarization modifying device, such as a liquid crystal variable retarder, and a controller. The polarization modifying device receives a laser beam and modifies the polarization of the laser beam. The...
Full text available at patent office. For more in-depth searching go to LexisNexis
view all 6 results from Patent Offices
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☐ **17.** LASER PROCESSING
LAUER, William / TREPANIER, Pierre / SMART, Donald, Victor / CORDINGLEY, James / PLOTKIN, Michael / GENERAL SCANNING, INC., *PATENT COOPERATION TREATY APPLICATION*, Jun 2000
The invention provides a system (10, 33) and method for vaporizing a target structure (24) on a substrate (22). According to the invention, a calculation is performed, as a function of wavelength, of an incident beam energy necessary to deposit unit...
Full text available at patent office. For more in-depth searching go to LexisNexis
view all 6 results from Patent Offices
similar results

☐ **18.** CONTROLLING LASER POLARIZATION
CORDINGLEY, James, J. / SMART, Donald, V. / PLOTKIN, Michael / LAUER, William / GENERAL SCANNING, INC., *PATENT COOPERATION TREATY APPLICATION*,

Jan 2000
A laser polarization control apparatus includes a polarization modifying device (24), such as a liquid crystal variable retarder, and a controller (18). The polarization modifying device receives a laser beam (12) and modifies the polarization of the...
Full text available at patent office. For more in-depth searching go to LexisNexis
view all 6 results from Patent Offices
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EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
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L2	2	("5366972" | "5705499").PN.	US-PGPUB; USPAT; USOCR	NEAR	ON	2006/08/01 12:44
L3	1	((MICHAEL) near2 (CORDINGLEY)).INV.	US-PGPUB; USPAT	NEAR	ON	2006/08/01 12:46
L4	3	(l1 or l2 or l3) and (ritonavir or (protease ADJ inhibitor))	US-PGPUB; USPAT	NEAR	ON	2006/08/01 12:47

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Last logoff:  31jul06 14:25:06
Logon file001 31jul06 15:04:43
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File   1:ERIC 1966-2006/June
       (c) format only 2006 Dialog

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       31jul06 15:04:46 User291213 Session D72.1
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     $0.39  Estimated cost File1
     $0.39  Estimated cost this search
     $0.39  Estimated total session cost   0.112 DialUnits


File   5:Biosis Previews(R) 1969-2006/Jul W4
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? s nnrti
      S1     577  NNRTI
? s ritonavir
      S2    2098  RITONAVIR
? s s1 and s2
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            2098  S2
      S3      59  S1 AND S2
? s s3 and cobmination()therapy
              59  S3
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          859743  THERAPY
               0  COBMINATION(W)THERAPY
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? s s3 and combination()therapy
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          325219  COMBINATION
          859743  THERAPY
           25599  COMBINATION(W)THERAPY
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        14135020  PY<2003
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 6/3,K/1
DIALOG(R)File   5:Biosis Previews(R)
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0014389108 BIOSIS NO.: 200300347827
Salvage therapy with lopinavir/ ritonavir **(LPV/r), amprenavir (APV) +- an additional boost with** ritonavir **(RTV) in HIV infected patients (pts) with multiple treatment failure: Final 26-week results of puzzle 1-ANRS104 Study.**
AUTHOR: Raguin G (Reprint); Chene G; Morand-Joubert L (Reprint); Taburet A; Droz C; Le Tiec C; Clavel F; Girard P (Reprint); Puzzle-1 Group
AUTHOR ADDRESS: Hosp St Antoine, Paris, France**France
JOURNAL: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 42 p267 2002 **2002**
MEDIUM: print
CONFERENCE/MEETING: 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy San Diego, CA, USA September 27-30, 2002; 20020927
SPONSOR: American Society for Microbiology
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

Salvage therapy with lopinavir/ ritonavir **(LPV/r), amprenavir (APV) +- an additional boost with** ritonavir **(RTV) in HIV infected patients (pts) with multiple treatment failure: Final 26-week results of...**
2002

...ABSTRACT: in pts with CD4+10,000 copies/ml after at least 2 PIs and 1 **NNRTI** . All pts were treated with LPV/r+APV and were randomized to receive or not...
...REGISTRY NUMBERS: **ritonavir** ;
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ... **ritonavir** --
...METHODS & EQUIPMENT: **combination therapy** --

6/3,K/2
DIALOG(R)File 5:Biosis Previews(R)

0014389092 BIOSIS NO.: 200300347811
Comparison of indinavir sulfate (IDV) 800 mg and ritonavir **(RTV) 100 mg b.i.d. +2 NRTIs vs. nelfinavir (NFV) 1250 mg b.i.d. +2 NRTIs in HIV-1 infected individuals who have failed or are intolerant to an** NNRTI **-containing regimen (Merck Protocol 112).**
AUTHOR: Bush L (Reprint); Novak R; Bohidar N; Rawlins S; Midgette P; Wilson H; Zeldin R
AUTHOR ADDRESS: South Florida Clinical Research, Atlantis, FL, USA**USA
JOURNAL: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 42 p263 2002 **2002**
MEDIUM: print
CONFERENCE/MEETING: 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy San Diego, CA, USA September 27-30, 2002; 20020927
SPONSOR: American Society for Microbiology
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

Comparison of indinavir sulfate (IDV) 800 mg and ritonavir **(RTV) 100 mg b.i.d. +2 NRTIs vs. nelfinavir (NFV) 1250 mg b.i...**
...2 NRTIs in HIV-1 infected individuals who have failed or are intolerant

to an NNRTI -containing regimen (Merck Protocol 112).
2002

...ABSTRACT: Increasingly, treatment of HIV-infected patients is being initiated with non-nucleoside reverse transcriptase inhibitors (**NNRTI**); however, treatment failures and cases of drug intolerance have been reported. This study compares the...

...label, randomized, multicenter, comparative, ongoing 48-week study in HIV-infected adults. Entry criteria included: **NNRTI** failure (initial viral response followed by viral (v) RNA >2000 copies, or vRNA never <400 copies) or intolerance (causing permanent discontinuation) to **NNRTI** therapy and CD4 gtoreq50 cells/mm3. Efficacy was evaluated using vRNA and CD4. As this...

...viral RNA than NFV 1250 mg bid +2 NRTIs in patients failing or intolerant of **NNRTI** therapy. Both regimens were generally well tolerated. Updated data will be presented.
...REGISTRY NUMBERS: **ritonavir** ;
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: **ritonavir** --
...METHODS & EQUIPMENT: **combination therapy** --

6/3,K/3
DIALOG(R)File 5:Biosis Previews(R)

0014389090 BIOSIS NO.: 200300347809
Final analysis of a randomised trial to evaluate safety and efficacy of indinavir/ ritonavir **versus saquinavir/** ritonavir **in adult HIV-1 infection: The MaxCmin1 Trial.**
AUTHOR: Gerstoft J (Reprint); Dragsted U B (Reprint); Cahn P (Reprint); Castagna A (Reprint); Duran A (Reprint); Hill A (Reprint); Pedersen C (Reprint); Peters B (Reprint); Vernazza P (Reprint); Youle M (Reprint); Lundgren J D (Reprint)
AUTHOR ADDRESS: Co-ordinating Office for the MaxCmin1 Trial, Copenhagen HIV Programme (CHIP), Copenhagen, Denmark**Denmark
JOURNAL: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 42 p263 2002 **2002**
MEDIUM: print
CONFERENCE/MEETING: 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy San Diego, CA, USA September 27-30, 2002; 20020927
SPONSOR: American Society for Microbiology
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

Final analysis of a randomised trial to evaluate safety and efficacy of indinavir/ ritonavir **versus saquinavir/** ritonavir **in adult HIV-1 infection: The MaxCmin1 Trial.**
2002

...ABSTRACT: treatment (Tx) effects are often unreliable. This is the first head-to-head comparison of **ritonavir** (r)-boosted protease inhibitor (PI) regimens. Methods: A 48 week open-label, randomised (1:1...

...a r-boosted PI Tx. The treating physician decided the concomitant use of >2 NRTI/ **NNRTI** prior to randomisation. Analysis are intention-to-treat on patients exposed to the randomised (R...
...REGISTRY NUMBERS: **ritonavir** ;
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: **ritonavir** --
...METHODS & EQUIPMENT: **combination therapy** --

6/3,K/4
DIALOG(R)File 5:Biosis Previews(R)

0014389087 BIOSIS NO.: 200300347806
Lopinavir/ ritonavir -efavirenz (LPV/r-EFV) NRTI-sparing regimen (BIKS study): Preliminary efficacy and safety data.
AUTHOR: Allavena C (Reprint); Raffi F (Reprint); Katlama C (Reprint); Delfraissy J (Reprint); Bentata M (Reprint); Lafeuillade A (Reprint); Michelet C (Reprint); Dellamonica P (Reprint); Launay O (Reprint)
AUTHOR ADDRESS: Hotel-Dieu, Nantes, France**France
JOURNAL: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 42 p262 2002 **2002**
MEDIUM: print
CONFERENCE/MEETING: 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy San Diego, CA, USA September 27-30, 2002; 20020927
SPONSOR: American Society for Microbiology
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Abstract
LANGUAGE: English

Lopinavir/ ritonavir -efavirenz (LPV/r-EFV) NRTI-sparing regimen (BIKS study): Preliminary éfficacy and safety data.
2002
...ABSTRACT: BID and EFV 600 mg QD in HIV-1-infected patients (pts). Pts should be **NNRTI** naive and, if PI-experienced, have less than 5 LPV/r-associated mutations (2001 French...
...REGISTRY NUMBERS: **ritonavir** ;
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ... **ritonavir** --
...METHODS & EQUIPMENT: **combination therapy** --

6/3,K/5
DIALOG(R)File 5:Biosis Previews(R)

0013886060 BIOSIS NO.: 200200479571
Differential modulation of P-glycoprotein expression and activity by non-nucleoside HIV-1 reverse transcriptase inhibitors in cell culture
AUTHOR: Stormer Elke; von Moltke Lisa L; Perloff Michael D; Greenblatt David J (Reprint)
AUTHOR ADDRESS: Department of Pharmacology and Experimental Therapeutics, Tufts University School of Medicine, Boston, MA, 02111, USA**USA
JOURNAL: Pharmaceutical Research (New York) 19 (7): p1038-1045 July, 2002 **2002**
MEDIUM: print
ISSN: 0724-8741

DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

2002

ABSTRACT: Purpose. This study investigated the effects of the non-nucleoside HIV-1 reverse transcriptase inhibitors (**NNRTI**) nevirapine (NVR), efavirenz (EFV), and delavirdine (DLV) on P-glycoprotein (P-gp) activity and expression to anticipate P-gp related drug-drug interactions associated with **combination therapy** . Methods. NNRTIs were evaluated as P-gp substrates by measuring differential transport across Caco-2...

...NNRTIs showed no differential transport between the basolateral to apical and apical to basolateral direction. **NNRTI** transport in either direction was not affected by the P-gp inhibitor verapamil. DLV inhibited ...

...and DLV were smaller. Acute DLV treatment of LS180V cells previously induced with NVR or **ritonavir** did not reverse the decreased Rh123 cell accumulation. Conclusions. NNRTIs show differential effects on P...

6/3,K/6
DIALOG(R)File 5:Biosis Previews(R)

0013097144 BIOSIS NO.: 200100268983
An open-label randomized trial to evaluate different therapeutic strategies of combination therapy **in HIV-1 infection: Design, rationale, and methods of the initio trial**
AUTHOR: Initio Co-ordinating Committee (Reprint)
AUTHOR ADDRESS: A. G. Babiker, MRC Clinical Trials Unit, 222 Euston Road, London, NW1 2DA, UK**UK
JOURNAL: Controlled Clinical Trials 22 (2): p160-175 April, 2001 **2001**
MEDIUM: print
ISSN: 0197-2456
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

An open-label randomized trial to evaluate different therapeutic strategies of combination therapy **in HIV-1 infection: Design, rationale, and methods of the initio trial**
2001

...ABSTRACT: d4T plus EFV plus NFV followed by ZDV plus 3TC plus ABC plus saquinavir plus **ritonavir** . The primary objective is to determine whether it is best to start with a protease inhibitor (PI)-containing regimen, a non-nucleoside analogue reverse transcriptase inhibitor (**NNRTI**)-containing regimen, or with a regimen containing both a PI and an **NNRTI** . The aim is to recruit over 1000 patients followed for at least 3 years. The...
? s ritonavir and (cyp or cytochrome?) and metabolism and bioavail?
2098 RITONAVIR
5287 CYP

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          109733  CYTOCHROME?
         3030373  METABOLISM
           32300  BIOAVAIL?
      S7      10  RITONAVIR AND (CYP OR CYTOCHROME?) AND METABOLISM AND
                  BIOAVAIL?
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      S8       7  S7 AND PY<2003
? s s8 not s6
               7  S8
               6  S6
      S9       7  S8 NOT S6
? t s9/5,k/all

 9/5,K/1
DIALOG(R)File   5:Biosis Previews(R)
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0014009207   BIOSIS NO.: 200200602718
Low systemic exposure of oral docetaxel in mice resulting from extensive
  first-pass metabolism is boosted by ritonavir
AUTHOR: Bardelmeijer Heleen A; Ouwehand Mariet; Buckle Tessa; Huisman
  Maarten T; Schellens Jan H M; Beijnen Jos H; Van Tellingen Olaf (Reprint)
AUTHOR ADDRESS: Department of Clinical Chemistry, Netherlands Cancer
  Institute/Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX,
  Amsterdam, Netherlands**Netherlands
JOURNAL: Cancer Research  62 (21): p6158-6164 November 1, 2002  2002
MEDIUM: print
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: P-glycoprotein seems to be the most important factor limiting the
  oral absorption of paclitaxel. We have now explored the mechanisms
  responsible for the low oral bioavailability of docetaxel, a
  structurally related taxane drug. The recovery of 33% of oxidative
  metabolites and only 39% of unchanged drug in the feces of FVB wild-type
  mice receiving 10 mg/kg of oral docetaxel indicates that the major part
  of the oral dose has been absorbed. The feces and bile of mice receiving
  10 mg/kg of i.v. docetaxel contained large amounts of metabolites and
  only minor quantities of unchanged drug, highlighting the importance of
  metabolism as an elimination route for this drug. In wild-type and
  P-glycoprotein knockout mice, dose escalation of p.o. administered
  docetaxel from 10 to 30 mg/kg resulted in a more than proportional
  increase in plasma levels, which suggested saturation of first-pass
  metabolism . Moreover, coadministration of 12.5 mg/kg of the HIV protease
  inhibitor ritonavir , also a strong inhibitor of cytochrome P4503A4
  with only minor P-glycoprotein inhibiting properties, increased the
  plasma levels after oral docetaxel by 50-fold. In vitro transport studies
  across monolayers of LLC-PK1 cells (parental and transduced with MDR1 or
  Mdr1a) suggested that docetaxel is a weaker substrate for P-glycoprotein
  than paclitaxel is. In conclusion, docetaxel is well absorbed from the
  gut lumen in mice despite the presence of P-glycoprotein in the gut wall.
  Subsequent first-pass extraction is the most important factor determining
  its low bioavailability . The inhibition of docetaxel metabolism by
```

ritonavir provides an interesting strategy to improve the systemic exposure of oral docetaxel.

REGISTRY NUMBERS: 114977-28-5: docetaxel; 33069-62-4: paclitaxel; 155213-67-5: **ritonavir**
DESCRIPTORS:
MAJOR CONCEPTS: **Metabolism** ; Pharmacology; Urinary System--Chemical Coordination and Homeostasis
BIOSYSTEMATIC NAMES: Muridae--Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Suidae--Artiodactyla, Mammalia, Vertebrata, Chordata, Animalia
ORGANISMS: mouse (Muridae)--animal model; LLC-PK1 cell line (Suidae)--pig renal cells
ORGANISMS: PARTS ETC: bile--digestive system; feces--digestive system
COMMON TAXONOMIC TERMS: Rodents; Animals; Artiodactyls; Chordates; Mammals; Nonhuman Vertebrates; Nonhuman Mammals; Vertebrates
CHEMICALS & BIOCHEMICALS: P-glycoprotein; docetaxel--antineoplastic-drug, low systemic exposure, oral administration, oral **bioavailability** ; paclitaxel--antineoplastic-drug; **ritonavir** --antiinfective-drug, antiviral-drug, human immunodeficiency virus protease inhibitor
MISCELLANEOUS TERMS: extensive first-pass **metabolism**
CONCEPT CODES:
02506 Cytology - Animal
10060 Biochemistry studies - General
10064 Biochemistry studies - Proteins, peptides and amino acids
10068 Biochemistry studies - Carbohydrates
12512 Pathology - Therapy
13002 Metabolism - General metabolism and metabolic pathways
14004 Digestive system - Physiology and biochemistry
15504 Urinary system - Physiology and biochemistry
22002 Pharmacology - General
24008 Neoplasms - Therapeutic agents and therapy
38502 Chemotherapy - General, methods and metabolism
38506 Chemotherapy - Antiviral agents
BIOSYSTEMATIC CODES:
86375 Muridae
85740 Suidae

Low systemic exposure of oral docetaxel in mice resulting from extensive first-pass metabolism **is boosted by** ritonavir
2002

...ABSTRACT: oral absorption of paclitaxel. We have now explored the mechanisms responsible for the low oral **bioavailability** of docetaxel, a structurally related taxane drug. The recovery of 33% of oxidative metabolites and...

...large amounts of metabolites and only minor quantities of unchanged drug, highlighting the importance of **metabolism** as an elimination route for this drug. In wild-type and P-glycoprotein knockout mice...

...in a more than proportional increase in plasma levels, which suggested saturation of first-pass **metabolism** . Moreover, coadministration of 12.5 mg/kg of the HIV protease inhibitor **ritonavir** , also a strong inhibitor of **cytochrome** P4503A4 with only minor P-glycoprotein inhibiting properties, increased the plasma levels after oral docetaxel...

...the gut wall. Subsequent first-pass extraction is the most important factor determining its low **bioavailability** . The inhibition of docetaxel **metabolism** by **ritonavir** provides an interesting strategy to improve the systemic exposure of oral docetaxel.
...REGISTRY NUMBERS: **ritonavir**
DESCRIPTORS:
MAJOR CONCEPTS: **Metabolism** ;
CHEMICALS & BIOCHEMICALS: ...antineoplastic-drug, low systemic exposure , oral administration, oral **bioavailability** ; ...

... **ritonavir** --
MISCELLANEOUS TERMS: extensive first-pass **metabolism**

9/5,K/2
DIALOG(R)File 5:Biosis Previews(R)

0013793234 BIOSIS NO.: 200200386745
Poor oral bioavailability **of clocetaxel in mice resulting from extensive first-pass** metabolism **is boosted by** ritonavir
AUTHOR: Bardelmeijer Heleen A (Reprint); Ouwehand Mariet; Buckle Tessa; Huisman Maarten T; Schellens Jan M; Beijnen Jos H; Van Tellingen Olaf
AUTHOR ADDRESS: Netherlands Cancer Institute, Amsterdam, Netherlands** Netherlands
JOURNAL: Proceedings of the American Association for Cancer Research Annual Meeting 43 p262-263 March, 2002 **2002**
MEDIUM: print
CONFERENCE/MEETING: 93rd Annual Meeting of the American Association for Cancer Research San Francisco, California, USA April 06-10, 2002; 20020406
ISSN: 0197-016X
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English
REGISTRY NUMBERS: 114977-28-5: docetaxel; 155213-67-5: **ritonavir**
DESCRIPTORS:
MAJOR CONCEPTS: **Metabolism** ; Pharmacology; Tumor Biology
BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae--Rodentia, Mammalia, Vertebrata, Chordata, Animalia; Suidae--Artiodactyla, Mammalia, Vertebrata, Chordata, Animalia
ORGANISMS: human (Hominidae); mouse (Muridae)--knockout; LLC-PK1 cell line (Suidae)--hampshire pig kidney epithelial cells
ORGANISMS: PARTS ETC: feces--digestive system; liver--digestive system; small intestine--digestive system
COMMON TAXONOMIC TERMS: Humans; Primates; Rodents; Animals; Artiodactyls; Chordates; Mammals; Nonhuman Vertebrates; Nonhuman Mammals; Vertebrates
CHEMICALS & BIOCHEMICALS: P-glycoprotein {P-gp}; **cytochrome** P450 iso-enzyme 3A4; docetaxel--antineoplastic-drug, oral administration, pharmacokinetics; **ritonavir** --enzyme inhibitor-drug, protease inhibitor-drug; tritiated docetaxel--antineoplastic-drug, pharmacokinetics
GENE NAME: mouse mdr1a/1b gene (Muridae)
MISCELLANEOUS TERMS: drug-drug interaction; Meeting Abstract; Meeting Abstract
CONCEPT CODES:

00520 General biology - Symposia, transactions and proceedings
02506 Cytology - Animal
02508 Cytology - Human
10060 Biochemistry studies - General
10064 Biochemistry studies - Proteins, peptides and amino acids
10068 Biochemistry studies - Carbohydrates
12512 Pathology - Therapy
13002 Metabolism - General metabolism and metabolic pathways
14004 Digestive system - Physiology and biochemistry
22002 Pharmacology - General
22003 Pharmacology - Drug metabolism and metabolic stimulators
22005 Pharmacology - Clinical pharmacology
24004 Neoplasms - Pathology, clinical aspects and systemic effects
24008 Neoplasms - Therapeutic agents and therapy
BIOSYSTEMATIC CODES:
86215 Hominidae
86375 Muridae
85740 Suidae

Poor oral bioavailability **of clocetaxel in mice resulting from extensive first-pass** metabolism **is boosted by** ritonavir
2002
...REGISTRY NUMBERS: **ritonavir**
DESCRIPTORS:
MAJOR CONCEPTS: **Metabolism** ;
CHEMICALS & BIOCHEMICALS: ... **cytochrome** P450 iso-enzyme 3A4...
... **ritonavir** --

9/5,K/3
DIALOG(R)File 5:Biosis Previews(R)

0013569409 BIOSIS NO.: 200200162920
CYP3A4-mediated hepatic metabolism **of the HIV-1 protease inhibitor saquinavir in vitro**
AUTHOR: Eagling V A; Wiltshire H; Whitcombe I W A; Back D J (Reprint)
AUTHOR ADDRESS: Department of Pharmacology and Therapeutics, University of Liverpool, Liverpool, L69 3GE, UK**UK
JOURNAL: Xenobiotica 32 (1): p1-17 January, 2002 **2002**
MEDIUM: print
ISSN: 0049-8254
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: 1. The aim was to identify the major metabolites of saquinavir (SQV) from human hepatic microsomal incubations and the **CYP** isoform(s) responsible. 2. Ten fractions containing various metabolites were separated by isocratic reversed-phase HPLC and characterized by HPLC, mass spectrometry and NMR. 3. Metabolites were either mono- or di-hydroxylated derivatives of SQV. Fast-atom bombardment and electrospray MS showed that hydroxylation was predominantly situated on the decahydroisoquinoline ring. A major metabolite (M4) was rigorously identified as 6-equatorial-hydroxy SQV. 4. **Metabolism** of saquinavir to all metabolites was inhibited by the CYP3A4-selective inhibitor ketoconazole (IC50 = 0.55 +- 0.12 muM). Other isoform-selective

inhibitors were non-inhibitory. The protease inhibitors **ritonavir** , indinavir and nelfinavir potently inhibited SQV **metabolism** in hepatic microsomes with IC50 = 0.025 +- 0.004, 0.82 +- 0.26 and 0.58 +- 0.14 muM, respectively. 5. Saquinavir **metabolism** correlated with immunochemically determined CYP3A4 levels and testosterone 6beta-hydroxylation, but it failed to correlate with either immunochemically determined CYP1A2 levels or marker activities for CYP1A2, 2C9 or 2E1. 6. Heterologously expressed CYP3A4 metabolized saquinavir with a similar metabolic profile to that of human liver microsomes. 7. Km and Vmax for total SQV **metabolism** were 0.61 +- 0.19 muM and 1.82 +- 1.13 nmol mg-1 min-1, respectively. 8. The extensive involvement of hepatic CYP3A4 in the **metabolism** of saquinavir predicts high intrinsic clearance of saquinavir. Inhibitors of CYP3A4 such as other protease inhibitors will substantially increase the **bioavailability** of saquinavir.

REGISTRY NUMBERS: 6329-61-9: decahydroisoquinoline; 150378-17-9: indinavir; 65277-42-1: ketoconazole; 159989-64-7: nelfinavir; 155213-67-5: **ritonavir** ; 127779-20-8: saquinavir; 58-22-0: testosterone

DESCRIPTORS:

MAJOR CONCEPTS: Digestive System--Ingestion and Assimilation; **Metabolism** ; Pharmacology

BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia; Retroviridae--DNA and RNA Reverse Transcribing Viruses, Viruses, Microorganisms

ORGANISMS: human (Hominidae); human immunodeficiency virus type 1 {HIV-1} (Retroviridae)--pathogen

ORGANISMS: PARTS ETC: hepatic microsome--digestive system

COMMON TAXONOMIC TERMS: Animals; Chordates; Humans; Mammals; Primates; Vertebrates; DNA and RNA Reverse Transcribing Viruses; Microorganisms; Viruses

CHEMICALS & BIOCHEMICALS: CYP1A2; CYP2C9; CYP2E1; CYP3A4; decahydroisoquinoline; indinavir--antiinfective-drug, antiviral-drug, enzyme inhibitor-drug, protease inhibitor-drug; ketoconazole; nelfinavir--antiinfective-drug, antiviral-drug, enzyme inhibitor-drug , protease inhibitor-drug; **ritonavir** --antiinfective-drug, antiviral-drug, enzyme inhibitor-drug, protease inhibitor-drug; saquinavir--antiinfective-drug, antiviral-drug, enzyme inhibitor-drug , protease inhibitor-drug, **bioavailability** , di-hydroxylated derivatives, mono-hydroxylated derivatives, pharmacokinetics; testosterone--6-beta-hydroxylation

METHODS & EQUIPMENT: NMR--Imaging Techniques, Spectrum Analysis Techniques, analytical method; isocratic reversed-phase high performance liquid chromatography--analytical method, separation method; mass spectrometry--Spectrum Analysis Techniques, analytical method

MISCELLANEOUS TERMS: hepatic **metabolism**

CONCEPT CODES:

10060 Biochemistry studies - General
10067 Biochemistry studies - Sterols and steroids
12512 Pathology - Therapy
13002 Metabolism - General metabolism and metabolic pathways
14004 Digestive system - Physiology and biochemistry
22002 Pharmacology - General
22003 Pharmacology - Drug metabolism and metabolic stimulators
22005 Pharmacology - Clinical pharmacology
33506 Virology - Animal host viruses
38502 Chemotherapy - General, methods and metabolism

38506 Chemotherapy - Antiviral agents
BIOSYSTEMATIC CODES:
86215 Hominidae
03305 Retroviridae

CYP3A4-mediated hepatic metabolism **of the HIV-1 protease inhibitor saquinavir in vitro**
2002

...ABSTRACT: to identify the major metabolites of saquinavir (SQV) from human hepatic microsomal incubations and the **CYP** isoform(s) responsible. 2. Ten fractions containing various metabolites were separated by isocratic reversed-phase...

...decahydroisoquinoline ring. A major metabolite (M4) was rigorously identified as 6-equatorial-hydroxy SQV. 4. **Metabolism** of saquinavir to all metabolites was inhibited by the CYP3A4-selective inhibitor ketoconazole (IC50 = 0.55 +- 0.12 muM). Other isoform-selective inhibitors were non-inhibitory. The protease inhibitors **ritonavir** , indinavir and nelfinavir potently inhibited SQV **metabolism** in hepatic microsomes with IC50 = 0.025 +- 0.004, 0.82 +- 0.26 and 0.58 +- 0.14 muM, respectively. 5. Saquinavir **metabolism** correlated with immunochemically determined CYP3A4 levels and testosterone 6beta-hydroxylation, but it failed to correlate...

...metabolic profile to that of human liver microsomes. 7. Km and Vmax for total SQV **metabolism** were 0.61 +- 0.19 muM and 1.82 +- 1.13 nmol mg-1 min-1, respectively. 8. The extensive involvement of hepatic CYP3A4 in the **metabolism** of saquinavir predicts high intrinsic clearance of saquinavir. Inhibitors of CYP3A4 such as other protease inhibitors will substantially increase the **bioavailability** of saquinavir.
...REGISTRY NUMBERS: **ritonavir** ;
DESCRIPTORS:
...MAJOR CONCEPTS: **Metabolism** ;
CHEMICALS & BIOCHEMICALS: ... **ritonavir** --...

...antiinfective-drug, antiviral-drug, enzyme inhibitor-drug, protease inhibitor-drug, **bioavailability** , di-hydroxylated derivatives, mono-hydroxylated derivatives, pharmacokinetics
MISCELLANEOUS TERMS: hepatic **metabolism**

9/5,K/4
DIALOG(R)File 5:Biosis Previews(R)

0013542979 BIOSIS NO.: 200200136490
Differentiation of gut and hepatic first-pass effect of drugs: 1. Studies of verapamil in ported dogs
AUTHOR: Lee Yong-Hee; Perry Barbara A; Lee Hee-Sang; Kunta Jeevan R; Sutyak John P; Sinko Patrick J (Reprint)
AUTHOR ADDRESS: Department of Pharmaceutics, College of Pharmacy, Rutgers University, Piscataway, NJ, 08854, USA**USA
JOURNAL: Pharmaceutical Research (New York) 18 (12): p1721-1728 December, 2001 **2001**
MEDIUM: print
ISSN: 0724-8741

DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Purpose. To investigate the relative contributions of the gut and liver to the first-pass loss of verapamil (VL) using an in vivo intestinal-vascular access port (IVAP) dog model. Methods. Basic pharmacokinetics of VL were determined after intravenous (IV: 0.5 mg/kg), portal venous (PV: 2 mg/kg), and duodenal (ID: 2 mg/kg) administration in IVAP dogs. Serial blood samples were collected for 8 h after dosing, and plasma was analyzed for unchanged drug by a high-performance liquid chromatography-fluorescence method. Extraction ratios in the liver and intestinal tract were determined from the area under the concentration-time curves for ID, PV, and IV administration. The functional role of CYP450 or secretory transporters such as P-gp on the gut and liver first-pass loss of VL was further studied using **ritonavir**, a known substrate or inhibitor of these processes. Results. The liver had a high intrinsic capacity for clearing VL because the absolute **bioavailability** (BA) of VL was 21.7% after PV administration. The BA of VL after ID administration was 23.5%; therefore, intestinal absorption was complete and intestinal extraction was negligible (ERGI apprx 0). The BA of VL increased from 23.5% to 66.2% in the presence of **ritonavir** primarily due to a reduction in hepatic extraction. Conclusions. Although the liver had a high intrinsic capacity for extracting VL, the contribution of gut to the first-pass loss of VL was negligible. Because of the additive effects of intestinal CYP3A-mediated **metabolism** and secretory transport, a significant gut first-pass effect was expected, but not observed in dogs. These studies demonstrate the utility of the in vivo IVAP dog model for evaluating the relative contribution of the gut and liver to the first-pass loss of drugs and for characterizing the functional role that CYP450 **metabolism** and/or secretory transporters play in drug-drug interactions and reduced oral **bioavailability**.

REGISTRY NUMBERS: 329736-03-0: **cytochrome** P450 3A4; 52-53-9: verapamil
DESCRIPTORS:
MAJOR CONCEPTS: **Metabolism** ; Pharmacology
BIOSYSTEMATIC NAMES: Canidae--Carnivora, Mammalia, Vertebrata, Chordata, Animalia
ORGANISMS: dog (Canidae)--model
ORGANISMS: PARTS ETC: gut--digestive system; liver--digestive system
COMMON TAXONOMIC TERMS: Animals; Carnivores; Chordates; Mammals; Nonhuman Vertebrates; Nonhuman Mammals; Vertebrates
CHEMICALS & BIOCHEMICALS: P-glycoprotein; **cytochrome** P450 3A4; verapamil--pharmaceutical
MISCELLANEOUS TERMS: pharmacokinetics
CONCEPT CODES:
10060 Biochemistry studies - General
10064 Biochemistry studies - Proteins, peptides and amino acids
10068 Biochemistry studies - Carbohydrates
12512 Pathology - Therapy
13002 Metabolism - General metabolism and metabolic pathways
14004 Digestive system - Physiology and biochemistry
22002 Pharmacology - General
22003 Pharmacology - Drug metabolism and metabolic stimulators
BIOSYSTEMATIC CODES:
85765 Canidae

2001

...ABSTRACT: gp on the gut and liver first-pass loss of VL was further studied using **ritonavir** , a known substrate or inhibitor of these processes. Results. The liver had a high intrinsic capacity for clearing VL because the absolute **bioavailability** (BA) of VL was 21.7% after PV administration. The BA of VL after ID...

...The BA of VL increased from 23.5% to 66.2% in the presence of **ritonavir** primarily due to a reduction in hepatic extraction. Conclusions. Although the liver had a high...

...pass loss of VL was negligible. Because of the additive effects of intestinal CYP3A-mediated **metabolism** and secretory transport, a significant gut first-pass effect was expected, but not observed in...

...to the first-pass loss of drugs and for characterizing the functional role that CYP450 **metabolism** and/or secretory transporters play in drug-drug interactions and reduced oral **bioavailability** .
...REGISTRY NUMBERS: **cytochrome** P450 3A4
DESCRIPTORS:
MAJOR CONCEPTS: **Metabolism** ;
CHEMICALS & BIOCHEMICALS: ... **cytochrome** P450 3A4

9/5,K/5
DIALOG(R)File 5:Biosis Previews(R)

0011549346 BIOSIS NO.: 199800343593
Metabolism **of the human immunodeficiency virus protease inhibitors indinavir and** ritonavir **by human intestinal microsomes and expressed** cytochrome **P4503A4/3A5: Mechanism-based inactivation of** cytochrome **P4503A by** ritonavir
AUTHOR: Koudriakova Tatiana (Reprint); Iatsimirskaia Eugenia; Utkin Ilya; Gangl Eric; Vouros Paul; Storozhuk Elena; Orza Daniela; Marinina Julia; Gerber Nicholas
AUTHOR ADDRESS: Dep. Pharmacology, Ohio State Univ., 5084 Graves Hall, 333 W. 10th Ave., Columbus, OH 43210, USA**USA
JOURNAL: Drug Metabolism and Disposition 26 (6): p552-561 June, 1998 **1998**
MEDIUM: print
ISSN: 0090-9556
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Both **ritonavir** and indinavir were readily metabolized by human intestinal microsomes. Comparison of the patterns of metabolites in incubations with enterocyte microsomes and expressed **cytochrome** P450 (**CYP**) isozymes and immunoinhibition and chemical inhibition studies showed the essential role of the CYP3A subfamily in the **metabolism** of both protease inhibitors by the small intestine. **Ritonavir** was similarly biotransformed by microsomes containing expressed CYP3A4 or CYP3A5 isozymes (KM = 0.050.07 muM, Vmax = 1-1.4 nmol/min/nmol **CYP**). In contrast, both the patterns of metabolites and the enzyme kinetic parameters for the **metabolism** of indinavir by expressed CYP3A5 (KM = 0.21 muM, Vmax = 0.24 nmol/min/nmol **CYP**) and CYP3A4 (KM = 0.04 muM,

Vmax = 0.68 nmol/min/nmol **CYP**) were different. The biotransformation of both indinavir and **ritonavir** in human enterocyte microsomes was characterized by very low KM values (0.2-0.4 muM for indinavir and <0.1 muM for **ritonavir**). The Vmax for indinavir **metabolism** was greater in enterocyte (163 +- 35 pmol/min/mg protein) than in liver (68 +- 44 pmol/min/mg protein) microsomes. The **metabolism** of **ritonavir** in liver and enterocyte microsomes was associated with inactivation of CYP3A. The initial Vmax for **ritonavir** **metabolism** by enterocyte microsomes was 89 +- 59 pmol/min/mg protein. The apparent inactivation rate constants for intestinal CYP3A and expressed CYP3A4 were 0.078 and 0.135 min-1, respectively. Metabolic inactivation of CYP3A by **ritonavir** explains the improved **bioavailability** and pharmacokinetics of **ritonavir** and the sustained elevation of blood levels of other, concomitantly administered, substrates of CYP3A.

REGISTRY NUMBERS: 329322-82-9: **cytochrome** P450 3A; 329736-03-0: **cytochrome** P450 3A4; 336874-97-6: **cytochrome** P450 3A5; 150378-17-9: indinavir; 155213-67-5: **ritonavir**

DESCRIPTORS:

MAJOR CONCEPTS: Pharmacology

BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGANISMS: human (Hominidae)

ORGANISMS: PARTS ETC: enterocytes--digestive system; intestinal microsomes--digestive system; liver--digestive system

COMMON TAXONOMIC TERMS: Animals; Chordates; Humans; Mammals; Primates; Vertebrates

CHEMICALS & BIOCHEMICALS: **cytochrome** P450 3A--inactivation; **cytochrome** P450 3A4; **cytochrome** P450 3A5; indinavir--protease inhibitor-drug, **metabolism** , pharmacokinetics; **ritonavir** --protease inhibitor-drug, **metabolism** , pharmacokinetics

CONCEPT CODES:

38502 Chemotherapy - General, methods and metabolism

02508 Cytology - Human

10060 Biochemistry studies - General

10802 Enzymes - General and comparative studies: coenzymes

13002 Metabolism - General metabolism and metabolic pathways

14001 Digestive system - General and methods

22002 Pharmacology - General

BIOSYSTEMATIC CODES:

86215 Hominidae

Metabolism **of the human immunodeficiency virus protease inhibitors indinavir and** ritonavir **by human intestinal microsomes and expressed** cytochrome **P4503A4/3A5: Mechanism-based inactivation of** cytochrome **P4503A by** ritonavir

1998

ABSTRACT: Both **ritonavir** and indinavir were readily metabolized by human intestinal microsomes. Comparison of the patterns of metabolites in incubations with enterocyte microsomes and expressed **cytochrome** P450 (**CYP**) isozymes and immunoinhibition and chemical inhibition studies showed the essential role of the CYP3A subfamily in the **metabolism** of both protease inhibitors by the small intestine. **Ritonavir** was similarly biotransformed by microsomes containing expressed CYP3A4 or CYP3A5 isozymes (KM = 0.050.07 muM, Vmax = 1-1.4 nmol/min/nmol **CYP**). In contrast, both the patterns of metabolites and the enzyme kinetic parameters for the **metabolism** of indinavir by expressed CYP3A5 (KM =

0.21 muM, Vmax = 0.24 nmol/min/nmol **CYP**) and CYP3A4 (KM = 0.04 muM, Vmax = 0.68 nmol/min/nmol **CYP**) were different. The biotransformation of both indinavir and **ritonavir** in human enterocyte microsomes was characterized by very low KM values (0.2-0.4 muM for indinavir and <0.1 muM for **ritonavir**). The Vmax for indinavir **metabolism** was greater in enterocyte (163 +- 35 pmol/min/mg protein) than in liver (68 +- 44 pmol/min/mg protein) microsomes. The **metabolism** of **ritonavir** in liver and enterocyte microsomes was associated with inactivation of CYP3A. The initial Vmax for **ritonavir** **metabolism** by enterocyte microsomes was 89 +- 59 pmol/min/mg protein. The apparent inactivation rate constants...

...CYP3A4 were 0.078 and 0.135 min-1, respectively. Metabolic inactivation of CYP3A by **ritonavir** explains the improved **bioavailability** and pharmacokinetics of **ritonavir** and the sustained elevation of blood levels of other, concomitantly administered, substrates of CYP3A.
...REGISTRY NUMBERS: **cytochrome** P450 3A...

... **cytochrome** P450 3A4...

... **cytochrome** P450 3A5...

... **ritonavir**
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: **cytochrome** P450 3A...

... **cytochrome** P450 3A4...

... **cytochrome** P450 3A5...

...protease inhibitor-drug, **metabolism** , pharmacokinetics...

... **ritonavir** --...

...protease inhibitor-drug, **metabolism** , pharmacokinetics

9/5,K/6
DIALOG(R)File 5:Biosis Previews(R)

0011481890 BIOSIS NO.: 199800276137
The effect of multiple doses of ritonavir **on the pharmacokinetics of rifabutin**
AUTHOR: Cato Allen III (Reprint); Cavanaugh John; Shi Harry; Hsu Ann; Leonard John; Granneman Richard
AUTHOR ADDRESS: Ligand Pharm. Inc., 10255 Science Centre Dr., San Diego, CA 92121, USA**USA
JOURNAL: Clinical Pharmacology and Therapeutics 63 (4): p414-421 April, 1998 **1998**
MEDIUM: print
ISSN: 0009-9236
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Objective. To investigate the effects of **ritonavir** on the pharmacokinetics of rifabutin. Methods. In a multiple-dose, randomized,

parallel-group, double-blind study, subjects received 150 mg rifabutin daily for 24 days coadministered on days 15 to 24 with twice-daily doses of either placebo or **ritonavir** (300 mg on day 15, 400 mg on day 16, and 500 mg on days 17 to 24). Plasma concentrations of rifabutin and 25-O-desacetylrifabutin were measured by HPLC, and the pharmacokinetics were determined after the rifabutin doses on days 14 and 24. Results. For subjects receiving rifabutin and placebo who completed the study (n = 11), there were small but statistically significant differences (ltoreq32%) in several rifabutin and 25-O-desacetylrifabutin pharmacokinetic parameters between the regimens of rifabutin alone and rifabutin with placebo. In contrast, the effect of **ritonavir** on rifabutin pharmacokinetics of subjects completing the study (n = 5) was substantial. Rifabutin mean minimum observed concentration (Cmin), maximum observed concentration (Cmin), and area under the concentration-time curve (AUC(0-24)) increased by approximately sixfold, 2.5-fold, and fourfold, respectively, and 25-O-desacetylrifabutin mean Cmin, Cmax, and AUC(0-24) increased by approximately 200-, 16-, and 35-fold, respectively, when coadministered with **ritonavir** compared with rifabutin administered alone. The sum of the mean AUC(0-24) of rifabutin and 25-O-desacetylrifabutin increased nearly sevenfold when coadministered with **ritonavir** . Conclusions. **Ritonavir** inhibited the **metabolism** of rifabutin and 25-O-desacetylrifabutin, suggesting that both are metabolized at least in part by CYP3A. **Ritonavir** may have enhanced rifabutin **bioavailability** by reducing either intestinal or hepatic **metabolism** or both. Clarithromycin is an alternative to rifabutin for antimycobacterial therapy that may be administered concurrently with **ritonavir** . Administration of **ritonavir** with a reduced rifabutin dosage regimen (150 mg every Monday, Wednesday, and Friday) is being investigated.

REGISTRY NUMBERS: 81103-11-9: clarithromycin; 72559-06-9: rifabutin; 155213-67-5: **ritonavir** ; 100324-63-8: 25-O-desacetylrifabutin

DESCRIPTORS:

MAJOR CONCEPTS: Pharmacology; Toxicology

BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGANISMS: human (Hominidae)

COMMON TAXONOMIC TERMS: Animals; Chordates; Humans; Mammals; Primates; Vertebrates

CHEMICALS & BIOCHEMICALS: clarithromycin--antibacterial-drug; rifabutin --antibacterial-drug, **bioavailability** , pharmacokinetics, combination therapy; **ritonavir** --antiviral-drug, combination therapy, dosage; CYP3A { **cytochrome** P450 3A}; 25-O-desacetylrifabutin

METHODS & EQUIPMENT: high performance liquid chromatography--analytical method

MISCELLANEOUS TERMS: drug-drug interaction

CONCEPT CODES:

22002 Pharmacology - General

10050 Biochemistry methods - General

10060 Biochemistry studies - General

10802 Enzymes - General and comparative studies: coenzymes

13002 Metabolism - General metabolism and metabolic pathways

22501 Toxicology - General and methods

38502 Chemotherapy - General, methods and metabolism

BIOSYSTEMATIC CODES:

86215 Hominidae

The effect of multiple doses of ritonavir **on the pharmacokinetics of rifabutin**
1998

ABSTRACT: Objective. To investigate the effects of **ritonavir** on the pharmacokinetics of rifabutin. Methods. In a multiple-dose, randomized, parallel-group, double-blind...

...days coadministered on days 15 to 24 with twice-daily doses of either placebo or **ritonavir** (300 mg on day 15, 400 mg on day 16, and 500 mg on days...

...between the regimens of rifabutin alone and rifabutin with placebo. In contrast, the effect of **ritonavir** on rifabutin pharmacokinetics of subjects completing the study (n = 5) was substantial. Rifabutin mean minimum...

...AUC(0-24) increased by approximately 200-, 16-, and 35-fold, respectively, when coadministered with **ritonavir** compared with rifabutin administered alone. The sum of the mean AUC(0-24) of rifabutin and 25-O-desacetylrifabutin increased nearly sevenfold when coadministered with **ritonavir** . Conclusions. **Ritonavir** inhibited the **metabolism** of rifabutin and 25-O-desacetylrifabutin, suggesting that both are metabolized at least in part by CYP3A. **Ritonavir** may have enhanced rifabutin **bioavailability** by reducing either intestinal or hepatic **metabolism** or both. Clarithromycin is an alternative to rifabutin for antimycobacterial therapy that may be administered concurrently with **ritonavir** . Administration of **ritonavir** with a reduced rifabutin dosage regimen (150 mg every Monday, Wednesday, and Friday) is being...
...REGISTRY NUMBERS: **ritonavir** ;
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ...antibacterial-drug, **bioavailability** , pharmacokinetics, combination therapy...

... **ritonavir** --...

...CYP3A { **cytochrome** P450 3A

9/5,K/7
DIALOG(R)File 5:Biosis Previews(R)

0011413478 BIOSIS NO.: 199800207725
Active apical secretory efflux of the HIV protease inhibitors saquinavir and ritonavir **in Caco-2 cell monolayers**
AUTHOR: Alsenz Jochem (Reprint); Steffen Hans; Alex Rainer
AUTHOR ADDRESS: PRNF, Build. 93/Room 7.10, F. Hoffmann-La Roche Ltd., Grenzacherstrasse, CH-4002 Basel, Switzerland**Switzerland
JOURNAL: Pharmaceutical Research (New York) 15 (3): p423-428 March, 1998
1998
MEDIUM: print
ISSN: 0724-8741
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Purpose. To investigate in vitro the mechanisms involved in the gastrointestinal absorption of the HIV protease inhibitor, saquinavir mesylate (Invirase), whose oral **bioavailability** is low, variable, and significantly increased by co-administration with **ritonavir** , also an HIV protease inhibitor but with higher oral **bioavailability** . Methods. Confluent epithelial layers of human Caco-2 cells mimicking the intestinal barrier. Results. Both saquinavir and **ritonavir** showed polarized transport through Caco-2 cell monolayers in the basolateral to apical direction (secretory pathway), exceeding apical to basolateral transport (absorptive pathway) by factors of 50-70 and 15-25, respectively. Active efflux was temperature dependent, saturable and inhibited by verapamil and cyclosporin A. Saquinavir and **ritonavir** decreased each other's secretory permeability and hence elevated their net transport by the absorptive pathway. Conclusions. Saquinavir and **ritonavir** are both substrates for an efflux mechanism in the gut, most likely P-glycoprotein, which acts as a counter-transporter for both drugs. Together with sensitivity to gut-wall **metabolism** by **cytochrome** P-450 3A, this may partially account for the low and variable oral **bioavailability** of saquinavir in clinical studies and for its increased **bioavailability** after co-administration with **ritonavir** .

REGISTRY NUMBERS: 329322-82-9: **cytochrome** P-450 3A; 144114-21-6: human immunodeficiency virus protease; 155213-67-5: **ritonavir** ; 149845-06-7: saquinavir mesylate

DESCRIPTORS:

MAJOR CONCEPTS: Dental and Oral System--Ingestion and Assimilation; Pharmacology

BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGANISMS: Caco-2 (Hominidae)

COMMON TAXONOMIC TERMS: Animals; Chordates; Humans; Mammals; Primates; Vertebrates

CHEMICALS & BIOCHEMICALS: **cytochrome** P-450 3A; human immunodeficiency virus protease; **ritonavir** --antiviral-drug, protease inhibitor-drug, gastrointestinal absorption, **bioavailability** ; saquinavir mesylate {Invirase}--antiviral-drug, protease inhibitor-drug, gastrointestinal absorption

MISCELLANEOUS TERMS: pharmaceuticals

CONCEPT CODES:

38506 Chemotherapy - Antiviral agents
02508 Cytology - Human
10806 Enzymes - Chemical and physical
14004 Digestive system - Physiology and biochemistry
10062 Biochemistry studies - Nucleic acids, purines and pyrimidines
10064 Biochemistry studies - Proteins, peptides and amino acids

BIOSYSTEMATIC CODES:

86215 Hominidae

Active apical secretory efflux of the HIV protease inhibitors saquinavir and ritonavir **in Caco-2 cell monolayers**
1998

...ABSTRACT: involved in the gastrointestinal absorption of the HIV protease inhibitor, saquinavir mesylate (Invirase), whose oral **bioavailability** is low, variable, and significantly increased by co-administration with **ritonavir** , also an HIV protease inhibitor but

with higher oral **bioavailability** . Methods. Confluent epithelial layers of human Caco-2 cells mimicking the intestinal barrier. Results. Both saquinavir and **ritonavir** showed polarized transport through Caco-2 cell monolayers in the basolateral to apical direction (secretory...

...Active efflux was temperature dependent, saturable and inhibited by verapamil and cyclosporin A. Saquinavir and **ritonavir** decreased each other's secretory permeability and hence elevated their net transport by the absorptive pathway. Conclusions. Saquinavir and **ritonavir** are both substrates for an efflux mechanism in the gut, most likely P-glycoprotein, which acts as a counter-transporter for both drugs. Together with sensitivity to gut-wall **metabolism** by **cytochrome** P-450 3A, this may partially account for the low and variable oral **bioavailability** of saquinavir in clinical studies and for its increased **bioavailability** after co-administration with **ritonavir** .
...REGISTRY NUMBERS: **cytochrome** P-450 3A...
... **ritonavir** ;
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: **cytochrome** P-450 3A...

... **ritonavir** --...

...antiviral-drug, protease inhibitor-drug, gastrointestinal absorption, **bioavailability** ;
? cost
31jul06 15:10:00 User291213 Session D72.2
$18.10 3.068 DialUnits File5
$12.30 6 Type(s) in Format 3
$14.35 7 Type(s) in Format 5
$26.65 13 Types
$44.75 Estimated cost File5
$1.60 TELNET
$46.35 Estimated cost this search
$46.74 Estimated total session cost 3.181 DialUnits

? logoff
31jul06 15:13:29 User291213 Session D72.2
$18.10 3.068 DialUnits File5
$12.30 6 Type(s) in Format 3
$14.35 7 Type(s) in Format 5
$26.65 13 Types
$44.75 Estimated cost File5
$2.40 TELNET
$47.15 Estimated cost this search
$47.54 Estimated total session cost 3.181 DialUnits

Logoff: level 05.12.03 D 15:13:29

You are now logged offDialog level 05.12.03D

Last logoff: 31jul06 15:13:29
Logon file001 31jul06 16:14:28
* * *

File 1:ERIC 1966-2006/June

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       (c) format only 2006 Dialog

      Set  Items  Description
      ---  -----  -----------
Cost is in DialUnits
?
Terminal set to DLINK
? s 5 71 34
      S1       0  5 71 34
? b 5 71 34
       31jul06 16:14:47 User291213 Session D73.1
            $0.73    0.209 DialUnits File1
     $0.73  Estimated cost File1
     $0.26  TELNET
     $0.99  Estimated cost this search
     $0.99  Estimated total session cost   0.209 DialUnits


SYSTEM:OS  - DIALOG OneSearch
  File   5:Biosis Previews(R) 1969-2006/Jul W4
         (c) 2006 The Thomson Corporation
  File  71:ELSEVIER BIOBASE 1994-2006/Jul W5
         (c) 2006  Elsevier Science B.V.
  File  34:SciSearch(R) Cited Ref Sci 1990-2006/Jul W4
         (c) 2006 The Thomson Corp

      Set  Items  Description
      ---  -----  -----------
? s nevirapi? or delavirid? or efaviren?
            3875  NEVIRAPI?
              28  DELAVIRID?
            2541  EFAVIREN?
      S1    5471  NEVIRAPI? OR DELAVIRID? OR EFAVIREN?
? s ritonav?
      S2    5259  RITONAV?
? s s1 and s2
            5471  S1
            5259  S2
      S3     860  S1 AND S2
? s cytochrome or cyp
          224748  CYTOCHROME
           13862  CYP
      S4  227610  CYTOCHROME OR CYP
? s s3 and s4
             860  S3
          227610  S4
      S5      70  S3 AND S4
? s metabolism
      S6 3617847  METABOLISM
? s s5 and s6
              70  S5
         3617847  S6
      S7      23  S5 AND S6
? rd
      S8      15  RD  (unique items)
? t s8/free/all
```

8/8/1 (Item 1 from file: 5)
0015139004 BIOSIS NO.: 200500045754
A valid option in the management of H.I.V. infection: Lopinavir- Ritonavir
ORIGINAL LANGUAGE TITLE: Una opcion vigente en el manejo de la infeccion por VIH: Lopinavir- **Ritonavir**
2004

8/8/2 (Item 2 from file: 5)
0014645109 BIOSIS NO.: 200400012093
Tipranavir: A protease inhibitor from a new class with distinct antiviral activity.
2003

8/8/3 (Item 3 from file: 5)
0014645098 BIOSIS NO.: 200400012082
Pharmacokinetic drug interactions with nevirapine .
2003

8/8/4 (Item 4 from file: 5)
0014519517 BIOSIS NO.: 200300473472
The role of clinical pharmacology in optimizing antiretroviral therapy.
2003

8/8/5 (Item 5 from file: 5)
0014099963 BIOSIS NO.: 200300058682
Population pharmacokinetic meta-analysis with efavirenz .
2002

8/8/6 (Item 6 from file: 5)
0014004816 BIOSIS NO.: 200200598327
Interactions between recreational drugs and antiretroviral agents
2002

8/8/7 (Item 7 from file: 5)
0012781827 BIOSIS NO.: 200000500140
ABT-378 and ritonavir **exposures are not predicted by erythromycin breath test (ERMBT)**
1999

8/8/8 (Item 8 from file: 5)
0012023537 BIOSIS NO.: 199900283197
Antiretroviral drug interactions
1998

8/8/9 (Item 9 from file: 5)
0011021199 BIOSIS NO.: 199799655259
Critical drug interactions with agents used for prophylaxis and treatment of Mycobacterium avium complex infections
1997

8/8/10 (Item 1 from file: 71)
01311641 1999052207
Drug interactions of HIV protease inhibitors

8/8/11 (Item 2 from file: 71)
00802210 1998038231
Systemic antifungal agents. Drug interactions of clinical significance
PUBLICATION DATE: 19980000

8/8/12 (Item 1 from file: 34)
DIALOG(R)File 34:(c) 2006 The Thomson Corp. All rts. reserv.

11182875 Genuine Article#: 618NF Number of References: 124
Title: Interactions between antiretroviral drugs and drugs used for the therapy of the metabolic complications encountered during HIV infection (ABSTRACT AVAILABLE)
Publication date: 20020000
Journal Subject Category: PHARMACOLOGY & PHARMACY
Identifiers--KeyWord Plus(R): IMMUNODEFICIENCY-VIRUS INFECTION; INCREASES PLASMA-CONCENTRATIONS; II RECEPTOR ANTAGONISTS; HUMAN-LIVER-MICROSOMES; IN-VITRO **METABOLISM** ; PROTEASE INHIBITORS; GRAPEFRUIT JUICE; CLINICAL PHARMACOKINETICS; INSULIN-RESISTANCE; **CYTOCHROME** -P450 ENZYMES

8/8/13 (Item 2 from file: 34)
DIALOG(R)File 34:(c) 2006 The Thomson Corp. All rts. reserv.

10838711 Genuine Article#: 574PZ Number of References: 44
Title: Differential modulation of P-glycoprotein expression and activity by non-nucleoside HIV-1 reverse transcriptase inhibitors in cell culture (ABSTRACT AVAILABLE)
Publication date: 20020700
Journal Subject Category: CHEMISTRY, MULTIDISCIPLINARY; PHARMACOLOGY & PHARMACY
Descriptors--Author Keywords: P-glycoprotein ; induction ; inhibition ; non-nucleoside reverse transcriptase inhibitors ; Caco-2 ; LS180
Identifiers--KeyWord Plus(R): MECHANISM-BASED INACTIVATION; COLON-CARCINOMA CELLS; PROTEASE INHIBITORS; TISSUE DISTRIBUTION; **CYTOCHROME** -P450 3A; CACO-2 CELLS; DRUG EFFLUX; **METABOLISM; RITONAVIR;** DELAVIRDINE

8/8/14 (Item 3 from file: 34)
DIALOG(R)File 34:(c) 2006 The Thomson Corp. All rts. reserv.

09319672 Genuine Article#: 393RH Number of References: 17
Title: Ritonavir , efavirenz , **and nelfinavir inhibit CYP2B6 activity in vitro: Potential drug interactions with bupropion** (ABSTRACT AVAILABLE)
Publication date: 20010200
Journal Subject Category: PHARMACOLOGY & PHARMACY
Identifiers--KeyWord Plus(R): DEPRESSIVE SYMPTOMS; PROTEASE INHIBITORS; HIV-INFECTION; **METABOLISM;** AIDS

8/8/15 (Item 4 from file: 34)
DIALOG(R)File 34:(c) 2006 The Thomson Corp. All rts. reserv.

07625207 Genuine Article#: 188UP Number of References: 26
Title: Paclitaxel in the treatment of human immunodeficiency virus 1-associated Kaposi's sarcoma - drug-drug interactions with protease inhibitors and a nonnucleoside reverse transcriptase inhibitor: a case report study (ABSTRACT AVAILABLE)
Publication date: 19990600
Journal Subject Category: PHARMACOLOGY & PHARMACY; ONCOLOGY
Descriptors--Author Keywords: antiretroviral agents ; Kaposi's sarcoma ; paclitaxel ; pharmacokinetics
Identifiers--KeyWord Plus(R): LIPOSOMAL DOXORUBICIN; CEREBROSPINAL-FLUID; HIV-INFECTION; HUMAN PLASMA; PHARMACOKINETICS; SAQUINAVIR; **RITONAVIR; METABOLISM;** MICROSOMES; SALIVA
? ds

Set	Items	Description
S1	5471	NEVIRAPI? OR DELAVIRID? OR EFAVIREN?
S2	5259	RITONAV?
S3	860	S1 AND S2
S4	227610	CYTOCHROME OR CYP
S5	70	S3 AND S4
S6	3617847	METABOLISM
S7	23	S5 AND S6
S8	15	RD (unique items)

? s s8/5,k/3,4,5,8
>>>Invalid syntax
? t s8/5,k/3,4,5,8

8/5,K/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2006 The Thomson Corporation. All rts. reserv.

0014645098 BIOSIS NO.: 200400012082
Pharmacokinetic drug interactions with nevirapine .
AUTHOR: Back David (Reprint); Gibbons Sara; Khoo Saye
AUTHOR ADDRESS: Liverpool HIV Pharmacology Group, Pharmacology Research Laboratories, University of Liverpool, Pembroke Place, Liverpool, L69 3GF, UK**UK
AUTHOR E-MAIL ADDRESS: daveback@liverpool.ac.uk
JOURNAL: JAIDS Journal of Acquired Immune Deficiency Syndromes 34 (Supplement 1): pS8-S14 September 2003 2003
MEDIUM: print
ISSN: 1525-4135 _(ISSN print)
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Treatment of HIV infection is a multi-drug issue. Not only are there drugs for the treatment of HIV but also concomitant drugs for opportunistic infections, complications arising from the anti-retroviral therapy and other conditions related to a chronic disease. To have any understanding of drug-drug interactions in HIV treatment we need to appreciate the importance of key pharmacological areas including: 1) how each drug in a regimen is eliminated; 2) the potential for a drug to either induce or inhibit metabolic enzymes and/or transporters; 3) the

therapeutic index of each drug. It is impossible to memorise all the possible drug-drug interactions in HIV, therefore understanding how drugs are metabolised/eliminated and the potential for a particular drug to modify the pharmacokinetics of another has predictive value even when substantive data are unavailable. NNRTIs interact with **cytochrome** P450 (CYP450) enzymes both as substrates and inducers. Because of the inductive effects caution must be exercised when using with pro tease inhibitors (either boosted or un-boosted with **ritonavir**). In this situation therapeutic drug monitoring may play a role in optimising response. There needs to be care when using many drugs with NNRTIs e.g. methadone, oral contraceptives, rifampicin, and there are some definite contraindications. By understanding pharmacological principles, it is possible to optimise use of multi-drug regimens.

REGISTRY NUMBERS: 9035-51-2: **cytochrome** P450; 154598-52-4: **efavirenz** ; 76-99-3: methadone; 129618-40-2: **nevirapine** ; 37205-61-1: protease inhibitors; 13292-46-1: rifampicin; 155213-67-5: **ritonavir**

DESCRIPTORS:

MAJOR CONCEPTS: Infection; Pharmacology

BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia; Retroviridae--DNA and RNA Reverse Transcribing Viruses, Viruses, Microorganisms

ORGANISMS: human (Hominidae)--patient; HIV {Human immunodeficiency virus} (Retroviridae)--pathogen

COMMON TAXONOMIC TERMS: Animals; Chordates; Humans; Mammals; Primates; Vertebrates; DNA and RNA Reverse Transcribing Viruses; Microorganisms; Viruses

DISEASES: HIV infection {human immunodeficiency virus infection}--blood and lymphatic disease, immune system disease, viral disease; opportunistic infection--infectious disease

MESH TERMS: HIV Infections (MeSH); Opportunistic Infections (MeSH)

CHEMICALS & BIOCHEMICALS: **cytochrome** P450 {CYP450}; **efavirenz** --antiinfective-drug, antiviral-drug; metabolic enzymes--induction, inhibition; metabolic transporters--induction, inhibition; methadone; **nevirapine** --antiinfective-drug, antiviral-drug, enzyme inhibitor-drug; oral contraceptives; protease inhibitors; rifampicin--antiinfective-drug; **ritonavir** --antiinfective-drug, antiviral-drug, enzyme inhibitor-drug, protease inhibitor-drug

METHODS & EQUIPMENT: anti-retroviral therapy--clinical techniques, therapeutic and prophylactic techniques; therapeutic drug monitoring--clinical techniques, therapeutic and prophylactic techniques

MISCELLANEOUS TERMS: disease chronicity; drug elimination; drug **metabolism** ; drug regimens; drug-drug interactions; herbals; key pharmacological areas; metabolic interactions; pharmacokinetic drug interactions; predictive value; response optimization; therapeutic index; Literature Review

CONCEPT CODES:

10060 Biochemistry studies - General
10802 Enzymes - General and comparative studies: coenzymes
12512 Pathology - Therapy
15006 Blood - Blood, lymphatic and reticuloendothelial pathologies
22002 Pharmacology - General
22005 Pharmacology - Clinical pharmacology
22028 Pharmacology - Reproductive system
33502 Virology - General and methods
34508 Immunology - Immunopathology, tissue immunology
36001 Medical and clinical microbiology - General and methods

36006 Medical and clinical microbiology - Virology
38502 Chemotherapy - General, methods and metabolism
38506 Chemotherapy - Antiviral agents
BIOSYSTEMATIC CODES:
86215 Hominidae
03305 Retroviridae
Pharmacokinetic drug interactions with nevirapine .

...ABSTRACT: pharmacokinetics of another has predictive value even when substantive data are unavailable. NNRTIs interact with **cytochrome** P450 (CYP450) enzymes both as substrates and inducers. Because of the inductive effects caution must be exercised when using with pro tease inhibitors (either boosted or un-boosted with **ritonavir**). In this situation therapeutic drug monitoring may play a role in optimising response. There needs...
...REGISTRY NUMBERS: **cytochrome** P450...

... **efavirenz** ; ...

... **nevirapine** ; ...

... **ritonavir**
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: **cytochrome** P450 {CYP450...

... **efavirenz** --...

... **nevirapine** --...

... **ritonavir** --
MISCELLANEOUS TERMS: ...drug **metabolism** ;

8/5,K/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014519517 BIOSIS NO.: 200300473472
The role of clinical pharmacology in optimizing antiretroviral therapy.
AUTHOR: Back David J (Reprint); Khoo Saye H
AUTHOR ADDRESS: Department of Pharmacology and Therapeutics, University of Liverpool, Ashton Street, Liverpool, L69 3BX, UK**UK
AUTHOR E-MAIL ADDRESS: D.J.Back@liverpool.ac.uk
JOURNAL: British Journal of Clinical Pharmacology 55 (5): p473-476 May 2003 2003
MEDIUM: print
ISSN: 0306-5251
DOCUMENT TYPE: Article
RECORD TYPE: Citation
LANGUAGE: English
REGISTRY NUMBERS: 329736-03-0: **cytochrome** P450 3A4; 154598-52-4: **efavirenz** ; 144114-21-6: human immunodeficiency virus protease; 150378-17-9: indinavir; 129618-40-2: **nevirapine** ; 37205-61-1: protease inhibitor; 155213-67-5: **ritonavir** ; 30516-87-1: zidovudine
DESCRIPTORS:
MAJOR CONCEPTS: Pharmacology
BIOSYSTEMATIC NAMES: Hominidae--Primates, Mammalia, Vertebrata, Chordata,

Animalia; Retroviridae--DNA and RNA Reverse Transcribing Viruses, Viruses, Microorganisms
ORGANISMS: human (Hominidae)--patient; Human immunodeficiency virus {HIV} (Retroviridae)--pathogen
ORGANISMS: PARTS ETC: plasma--blood and lymphatics
COMMON TAXONOMIC TERMS: Animals; Chordates; Humans; Mammals; Primates; Vertebrates; DNA and RNA Reverse Transcribing Viruses; Microorganisms; Viruses
DISEASES: human immunodeficiency virus infection {HIV infection}--blood and lymphatic disease, immune system disease, viral disease, drug therapy
MESH TERMS: HIV Infections (MeSH)
CHEMICALS & BIOCHEMICALS: CD4; **cytochrome** P450 3A4; **efavirenz** -- antiinfective-drug, antiviral-drug; human immunodeficiency virus protease; indinavir--antiinfective-drug, antiviral-drug, enzyme inhibitor-drug, protease inhibitor-drug; **nevirapine** -- antiinfective-drug, antiviral-drug, enzyme inhibitor-drug; non-nucleoside reverse transcriptase inhibitors--antiinfective-drug, antiviral-drug, enzyme inhibitor-drug, reverse transcriptase inhibitor-drug, pharmacokinetics; nucleoside reverse transcriptase inhibitor--antiinfective-drug, antiviral-drug, enzyme inhibitor-drug, reverse transcriptase inhibitor-drug, pharmacokinetics; protease inhibitor--antiinfective-drug, antiviral-drug, enzyme inhibitor-drug, protease inhibitor-drug, pharmacokinetics; **ritonavir** -- antiinfective-drug, antiviral-drug, enzyme inhibitor-drug, protease inhibitor-drug; zidovudine--antiinfective-drug, antiviral-drug, enzyme inhibitor-drug, reverse transcriptase inhibitor-drug, pharmacokinetics
METHODS & EQUIPMENT: antiretroviral therapy--clinical techniques, therapeutic and prophylactic techniques; highly active antiretroviral therapy {HAART}--clinical techniques, therapeutic and prophylactic techniques; therapeutic drug monitoring--clinical techniques
GEOGRAPHICAL NAME: sub-Saharan Africa (Africa) (Ethiopian region) (Palearctic region)
MISCELLANEOUS TERMS: antiretroviral therapy optimization; clinical pharmacology; drug **metabolism** ; pharmacogenomics; treatment failure

CONCEPT CODES:
10060 Biochemistry studies - General
10062 Biochemistry studies - Nucleic acids, purines and pyrimidines
10064 Biochemistry studies - Proteins, peptides and amino acids
12512 Pathology - Therapy
15002 Blood - Blood and lymph studies
15004 Blood - Blood cell studies
15006 Blood - Blood, lymphatic and reticuloendothelial pathologies
22002 Pharmacology - General
22003 Pharmacology - Drug metabolism and metabolic stimulators
22005 Pharmacology - Clinical pharmacology
33502 Virology - General and methods
34508 Immunology - Immunopathology, tissue immunology
36006 Medical and clinical microbiology - Virology
38502 Chemotherapy - General, methods and metabolism
38506 Chemotherapy - Antiviral agents

BIOSYSTEMATIC CODES:
86215 Hominidae
03305 Retroviridae

...REGISTRY NUMBERS: **cytochrome** P450 3A4...

... **efavirenz** ; ...

... **nevirapine** ; ...

... **ritonavir** ;
DESCRIPTORS:
  CHEMICALS & BIOCHEMICALS: ... **cytochrome** P450 3A4...

... **efavirenz** --...
... **nevirapine** --...

... **ritonavir** --
  MISCELLANEOUS TERMS: ...drug **metabolism** ;

8/5,K/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0014099963 BIOSIS NO.: 200300058682
Population pharmacokinetic meta-analysis with efavirenz .
AUTHOR: Barrett J S (Reprint); Joshi A S; Chai M; Ludden T M; Fiske W D; Pieniaszek H J
AUTHOR ADDRESS: Aventis Pharmaceuticals, Route 202-206, PO Box 6800, Bridgewater, NJ, 08807, USA**USA
AUTHOR E-MAIL ADDRESS: jeff.barrett@aventis.com
JOURNAL: International Journal of Clinical Pharmacology and Therapeutics 40 (11): p507-519 November 2002 2002
MEDIUM: print
ISSN: 0946-1965
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A population-based pharmacokinetic (PK) model has been developed for **efavirenz** based on 16 phase I studies. The combined data set consisted of 334 healthy volunteers, 2,907 **efavirenz** dose administrations and 9,342 measured plasma concentrations across a range of doses from 100-600 mg. The pharmacokinetic structural model was a 2-compartment model with first-order absorption with differentiation between single- and multiple-dose exposure to account for known hepatic **cytochrome** P450 induction of **efavirenz** **metabolism** . Model-building was performed on the index data set (66% of the total database), as a data-splitting technique was used to validate the final model using NONMEM. The final model confirmed the appropriateness of separate clearance terms for single and multiple dose administration (2.65 versus 10.2 l/h, respectively). Clearance increased with dose and frequency of administration. A lower clearance was predicted in Asians and Blacks relative to Caucasians. A slightly lower clearance was observed in females relative to males (9.08 compared to 10.2 l/h in males) and interactions on clearance due to co-administration of fluconazole, **ritonavir** , rifampin, indinavir and azithromycin were identified. The magnitudes of these effects were small and did not suggest dose adjustment in the various sub-populations. With little exception, these results agree with the findings from the non-compartmental analyses. The residual variability was 21% CV and the intersubject variation in CL/F

and V/F was 48 and 85%, respectively. The phase I meta-analysis was able to substantiate the pharmacokinetic characteristics of **efavirenz** derived from the composite of individual well-defined studies. The model was deemed adequate for subsequent evaluation in HIV-infected patients. Covariates and outlier classes identified in this phase I meta-analysis were similarly identified in subsequent analyses of patient data.

REGISTRY NUMBERS: 154598-52-4: **efavirenz** ; 86386-73-4: fluconazole; 155213-67-5: **ritonavir** ; 13292-46-1: rifampin; 150378-17-9: indinavir; 83905-01-5: azithromycin

DESCRIPTORS:

MAJOR CONCEPTS: Pharmacology

BIOSYSTEMATIC NAMES: Retroviridae--DNA and RNA Reverse Transcribing Viruses, Viruses, Microorganisms; Hominidae--Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGANISMS: HIV {Human immunodeficiency virus} (Retroviridae)--pathogen; human (Hominidae)

COMMON TAXONOMIC TERMS: DNA and RNA Reverse Transcribing Viruses; Microorganisms; Viruses; Animals; Chordates; Humans; Mammals; Primates; Vertebrates

DISEASES: HIV infection {human immunodeficiency virus infection}--blood and lymphatic disease, immune system disease, viral disease

MESH TERMS: HIV Infections (MeSH)

CHEMICALS & BIOCHEMICALS: **efavirenz** --antiinfective-drug, antiviral-drug, enzyme inhibitor-drug, reverse transcriptase inhibitor-drug; fluconazole--antifungal-drug, antiinfective-drug; **ritonavir** --antiinfective-drug, antiviral-drug, enzyme inhibitor-drug , protease inhibitor-drug; rifampin--antibacterial-drug, antiinfective-drug, enzyme inhibitor-drug; indinavir--antiinfective-drug, antiviral-drug, enzyme inhibitor-drug, protease inhibitor-drug; azithromycin--antibacterial-drug, antiinfective-drug

METHODS & EQUIPMENT: population pharmacokinetic meta-analysis--mathematical and computer techniques

CONCEPT CODES:

10060 Biochemistry studies - General
12512 Pathology - Therapy
15006 Blood - Blood, lymphatic and reticuloendothelial pathologies
22002 Pharmacology - General
22005 Pharmacology - Clinical pharmacology
33502 Virology - General and methods
34508 Immunology - Immunopathology, tissue immunology
36006 Medical and clinical microbiology - Virology
38502 Chemotherapy - General, methods and metabolism
38504 Chemotherapy - Antibacterial agents
38506 Chemotherapy - Antiviral agents
38508 Chemotherapy - Antifungal agents

BIOSYSTEMATIC CODES:

03305 Retroviridae
86215 Hominidae

Population pharmacokinetic meta-analysis with efavirenz .

ABSTRACT: A population-based pharmacokinetic (PK) model has been developed for **efavirenz** based on 16 phase I studies. The combined data set consisted of 334 healthy volunteers, 2,907 **efavirenz** dose administrations and 9,342 measured plasma concentrations across a range of doses from 100...

...order absorption with differentiation between single- and multiple-dose exposure to account for known hepatic **cytochrome** P450 induction of **efavirenz** **metabolism** . Model-building was performed on the index data set (66% of the total database), as...

...2 l/h in males) and interactions on clearance due to co-administration of fluconazole, **ritonavir** , rifampin, indinavir and azithromycin were identified. The magnitudes of these effects were small and did...

...85%, respectively. The phase I meta-analysis was able to substantiate the pharmacokinetic characteristics of **efavirenz** derived from the composite of individual well-defined studies. The model was deemed adequate for...
...REGISTRY NUMBERS: **efavirenz** ; ...

... **ritonavir** ;
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: **efavirenz** --...

... **ritonavir** --

8/5,K/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

0012023537 BIOSIS NO.: 199900283197
Antiretroviral drug interactions
AUTHOR: Flexner Charles (Reprint)
AUTHOR ADDRESS: Johns Hopkins Univ., Baltimore, MD, USA**USA
JOURNAL: Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy 38 p641 1998 1998
MEDIUM: print
CONFERENCE/MEETING: 38th Interscience Conference on Antimicrobial Agents and Chemotherapy San Diego, California, USA September 24-27, 1998; 19980924
SPONSOR: American Society for Microbiology
DOCUMENT TYPE: Meeting; Meeting Abstract
RECORD TYPE: Citation
LANGUAGE: English
REGISTRY NUMBERS: 161814-49-9: amprenavir; 9035-51-2: **cytochrome** P450; 136817-59-9: delavirdine; 154598-52-4: **efavirenz** ; 150378-17-9: indinavir; 159989-64-7: nelfinavir; 129618-40-2: **nevirapine** ; 155213-67-5: **ritonavir** ; 127779-20-8: saquinavir; 144114-21-6: HIV protease
DESCRIPTORS:
MAJOR CONCEPTS: Pharmacology
CHEMICALS & BIOCHEMICALS: amprenavir--antiviral-drug, enzyme inhibitor-drug, pharmacokinetics; clopidogreal {viagra}--antiviral-drug ; **cytochrome** P450--oxidative **metabolism** ; delavirdine--antiviral-drug, enzyme inhibitor-drug, pharmacokinetics; **efavirenz** --antiviral-drug, enzyme inhibitor-drug, pharmacokinetics; indinavir--antiviral-drug, enzyme inhibitor-drug, pharmacokinetics; nelfinavir--antiviral-drug, enzyme inhibitor-drug, pharmacokinetics; **nevirapine** --enzyme inhibitor-drug, pharmacokinetics; non-nucleoside reverse transcriptase--inhibition; **ritonavir** --antiviral-drug, enzyme inhibitor-drug, pharmacokinetics; saquinavir--antiviral-drug, enzyme

inhibitor-drug, pharmacokinetics; HIV protease {human immunodeficiency virus protease}--inhibition
MISCELLANEOUS TERMS: drug-drug interactions; Meeting Abstract; Meeting Abstract
CONCEPT CODES:
22002 Pharmacology - General
10802 Enzymes - General and comparative studies: coenzymes
13002 Metabolism - General metabolism and metabolic pathways
38502 Chemotherapy - General, methods and metabolism
00520 General biology - Symposia, transactions and proceedings

...REGISTRY NUMBERS: **cytochrome** P450...
... **efavirenz** ; ...

... **nevirapine** ; ...

... **ritonavir** ;
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ... **cytochrome** P450...

...oxidative **metabolism** ; ...

... **efavirenz** --...

... **nevirapine** --...

... **ritonavir** --
? cost
31jul06 16:19:14 User291213 Session D73.2
$3.91 0.662 DialUnits File5
$8.20 4 Type(s) in Format 5
$0.00 9 Type(s) in Format 6
$8.20 13 Types
$12.11 Estimated cost File5
$3.34 0.380 DialUnits File71
$0.00 2 Type(s) in Format 6
$0.00 2 Types
$3.34 Estimated cost File71
$10.44 0.445 DialUnits File34
$0.00 4 Type(s) in Format 8
$0.00 4 Types
$10.44 Estimated cost File34
OneSearch, 3 files, 1.487 DialUnits FileOS
$1.33 TELNET
$27.22 Estimated cost this search
$28.21 Estimated total session cost 1.696 DialUnits

? logoff
31jul06 16:22:10 User291213 Session D73.2
$3.91 0.662 DialUnits File5
$8.20 4 Type(s) in Format 5
$0.00 9 Type(s) in Format 6
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$12.11 Estimated cost File5
$3.34 0.380 DialUnits File71
$0.00 2 Type(s) in Format 6
$0.00 2 Types

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     $3.34  Estimated cost File71
           $10.44    0.445 DialUnits File34
               $0.00  4 Type(s) in Format  8
            $0.00  4 Types
    $10.44  Estimated cost File34
            OneSearch, 3 files,  1.487 DialUnits FileOS
     $2.13  TELNET
    $28.02  Estimated cost this search
    $29.01  Estimated total session cost   1.696 DialUnits


Logoff: level 05.12.03 D  16:22:10


You are now logged offDialog level 05.12.03D

Last logoff:  31jul06 16:22:10
Logon file001 31jul06 16:46:22
* * *

File   1:ERIC 1966-2006/June
       (c) format only 2006 Dialog

      Set  Items  Description
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Cost is in DialUnits
?
Terminal set to DLINK
? b 5 71 34 155
       31jul06 16:46:38 User291213 Session D74.1
            $0.38    0.107 DialUnits File1
     $0.38  Estimated cost File1
     $0.06  TELNET
     $0.44  Estimated cost this search
     $0.44  Estimated total session cost   0.107 DialUnits


SYSTEM:OS  - DIALOG OneSearch
  File   5:Biosis Previews(R) 1969-2006/Jul W4
         (c) 2006 The Thomson Corporation
  File  71:ELSEVIER BIOBASE 1994-2006/Jul W5
         (c) 2006  Elsevier Science B.V.
  File  34:SciSearch(R) Cited Ref Sci 1990-2006/Jul W4
         (c) 2006 The Thomson Corp
  File 155:MEDLINE(R) 1950-2006/Jul 31
         (c) format only 2006 Dialog

      Set  Items  Description
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? s au=mummaneni
      S1       0  AU=MUMMANENI
? s mummaneni
      S2       7  MUMMANENI
? s s2 and efavrienz
               7  S2
               0  EFAVRIENZ
      S3       0  S2 AND EFAVRIENZ
```

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? s au=(mummaneni)
      S4        0  AU=(MUMMANENI)
? s efavirenz
      S5     3640  EFAVIRENZ
? s ritonavir and afazanavir
             7379  RITONAVIR
                0  AFAZANAVIR
      S6        0  RITONAVIR AND AFAZANAVIR
? s ritonavir and atazanavir
             7379  RITONAVIR
              721  ATAZANAVIR
      S7      369  RITONAVIR AND ATAZANAVIR
? ds

Set     Items   Description
S1          0   AU=MUMMANENI
S2          7   MUMMANENI
S3          0   S2 AND EFAVRIENZ
S4          0   AU=(MUMMANENI)
S5       3640   EFAVIRENZ
S6          0   RITONAVIR AND AFAZANAVIR
S7        369   RITONAVIR AND ATAZANAVIR
? s s5 and s7
             3640  S5
              369  S7
      S8      119  S5 AND S7
? s s8 and pharmacokinetic
              119  S8
           128051  PHARMACOKINETIC
      S9       13  S8 AND PHARMACOKINETIC
? rd
     S10        8  RD  (unique items)
? s s10/5,k/all
>>>Invalid syntax
? t s10/5,k/all

 10/5,K/1     (Item 1 from file: 71)
DIALOG(R)File  71:ELSEVIER BIOBASE
(c) 2006  Elsevier Science B.V. All rts. reserv.

03405067        2006191078
Influence of tenofovir, nevirapine and efavirenz on ritonavir -boosted
  atazanavir pharmacokinetics in HIV-infected patients
Dailly E.; Tribut O.; Tattevin P.; Arvieux C.; Perre P.; Raffi F.; Jolliet
P.
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         Moncousu, 44093 Nantes, Cedex, France
EMAIL: eric.dailly@chu-nantes.fr
Journal: European Journal of Clinical Pharmacology, 62/7 (523-526), 2006,
         Germany
CODEN: EJCPA
ISSN: 0031-6970
DOCUMENT TYPE: Article
LANGUAGES: English       SUMMARY LANGUAGES: English
NO. OF REFERENCES: 11

Objective: The influence of nevirapine, efavirenz and tenofovir
```

co-administration on **ritonavir** -boosted **atazanavir** pharmacokinetics was investigated in HIV (human immunodeficiency virus)-infected patients. Methods: A population **pharmacokinetic** analysis was performed in the context of therapeutic drug monitoring (87 patients, 121 samples). Results: A significant increase of **atazanavir** clearance (Cl/F) was found when either tenofovir (group B), **efavirenz** (group C), or nevirapine (group D) were co administered with **atazanavir / ritonavir** in comparison with patients treated with **atazanavir / ritonavir** and nucleoside reverse transcriptase inhibitors (group A): 6.24+/-0.36 l hSUP-1 (group A) versus 7.42+/-0.25 l h SUP-1 (group B) versus 9.60+/-0.27 l hSUP-1 (group C) versus 17.53+/-0.57 l hSUP-1 (group D) (P<0.001). However, the decrease of the mean trough plasma concentration of **atazanavir** was significant only in group D: 1.02+/-0.86 mg/l (group A) versus 0.21+/-013 mg/l (group D) (P<0.001). Conclusion: The increase in **atazanavir** clearance when it is used in combination with nevirapine, **efavirenz** and/or tenofovir suggests that therapeutic drug monitoring of **atazanavir** should be performed in such circumstances. (c) Springer-Verlag 2006.

DESCRIPTORS:
Atazanavir ; Nevirapine; **Efavirenz** ; Tenofovir; Pharmacokinetics; Interaction

CLASSIFICATION CODE AND DESCRIPTION:
99 - General

Influence of tenofovir, nevirapine and efavirenz **on** ritonavir **-boosted** atazanavir **pharmacokinetics in HIV-infected patients**

Objective: The influence of nevirapine, **efavirenz** and tenofovir co-administration on **ritonavir** -boosted **atazanavir** pharmacokinetics was investigated in HIV (human immunodeficiency virus)-infected patients. Methods: A population **pharmacokinetic** analysis was performed in the context of therapeutic drug monitoring (87 patients, 121 samples). Results: A significant increase of **atazanavir** clearance (Cl/F) was found when either tenofovir (group B), **efavirenz** (group C), or nevirapine (group D) were co administered with **atazanavir / ritonavir** in comparison with patients treated with **atazanavir / ritonavir** and nucleoside reverse transcriptase inhibitors (group A): 6.24+/-0.36 l hSUP-1 (group...

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DESCRIPTORS:
Atazanavir ; Nevirapine; **Efavirenz** ; Tenofovir; Pharmacokinetics; Interaction

10/5,K/2 (Item 2 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE

03150949 2005292794

Atazanavir : **A review of its use in the management of HIV infection**

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Journal: Drugs, 65/16 (2309-2336), 2005, New Zealand
CODEN: DRUGA
ISSN: 0012-6667
DOCUMENT TYPE: Review
LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 77

Abstract: **Atazanavir** (Reyataz(R)) is a novel protease inhibitor (PI) approved for use in combination with other antiretroviral drugs for the treatment of HIV infection. In antiretroviral therapy (ART)-experienced patients the drug is administered with low-dose **ritonavir** (i.e. boosted). In the US, unboosted **atazanavir** is also approved for use in ART-naive patients. In adult patients with HIV infection, **atazanavir** -containing highly active antiretroviral therapy (HAART) regimens provided marked improvements in virological and immunological markers and was generally well tolerated. Furthermore, recommended **atazanavir** regimens were no less effective than, and generally as well tolerated as, other HAART regimens in these patients, including regimens containing co-formulated lopinavir/ **ritonavir** . **Atazanavir** may have an advantage over other PIs because of its favourable effect on lipid profiles, once-daily dosing, low capsule burden and, in patients with low prior PI exposure, a favourable resistance profile. Given these advantages and taking into consideration between-country differences in the approved indications, **atazanavir** is a valuable option as the PI component of HAART for the management of HIV infection in adult ART-naive patients, particularly where metabolic complications are a concern, and as a first- or second-line PI in combination with low-dose **ritonavir** in adult ART-experienced patients. Pharmacological Properties: **Atazanavir** prevents the formation of mature virions by inhibiting the processing of viral gag and gag-pol polyproteins in HIV-infected cells. The unique, signature mutation for **atazanavir** resistance in isolates from ART-naive patients was an isoleucine to leucine substitution at amino acid residue 50 of the HIV-1 protease gene. This mutation was **atazanavir** -specific and conferred increased susceptibility to other PIs. However, in ART-experienced patients who had never previously received **atazanavir** , **atazanavir** susceptibility was reduced in the presence of multiple mutations associated with resistance to other PIs. There was high cross-resistance to **atazanavir** in patients with prior exposure to at least three other PIs. Limited data suggest that **atazanavir** -containing regimens were not associated with insulin resistance, and evidence from clinical trials showed that **atazanavir** had a lower propensity to cause dyslipidaemia than nelfinavir or **efavirenz** in ART-naive patients or lopinavir/ **ritonavir** in ART-experienced patients. Moreover, ART-experienced patients with hyperlipidaemia receiving **atazanavir** -containing therapy experienced reductions from baseline in total cholesterol, non-high-density lipoprotein cholesterol and trigylceride levels. The pharmacokinetics of oral **atazanavir** administered once daily are non-linear. Greater **atazanavir** exposure was observed in healthy volunteers than in patients with HIV infection. Boosting with low-dose **ritonavir** increases **atazanavir** plasma trough concentrations (the pharmacodynamically linked variable) because of the **pharmacokinetic** interaction between these drugs. The terminal elimination half-life of unboosted **atazanavir** was approximately 7 hours in patients with HIV

infection or healthy volunteers. The hepatic cytochrome P450 3A isoenzyme metabolises **atazanavir** to pharmacologically inactive metabolites that are, along with the unchanged drug, eliminated primarily via the biliary pathway. **Pharmacokinetic** drug interactions between **atazanavir** and numerous coadministered drugs, including certain antiretroviral drugs, antimycobacterials, calcium channel antagonists, oral contraceptives and proton pump inhibitors, have been demonstrated. Therapeutic Efficacy: In phase II or III trials in ART-naive patients receiving a dual-nucleoside reverse transcriptase inhibitor (NRTI)-containing regimen, the efficacy of **atazanavir** 400mg once daily was similar to that of nelfinavir 750mg three times daily, nelfinavir 1250mg twice daily or **efavirenz** 600mg once daily after 48 weeks' treatment. Viral suppression was maintained for an additional 24 weeks in an open-label extension study. In a randomised 48-week phase III trial in patients also receiving two NRTIs, who had previously failed two HAART regimens, the efficacy of **atazanavir** 300mg once daily boosted with **ritonavir** 100mg once daily was noninferior to that of co-formulated lopinavir/ **ritonavir** 400mg/100mg twice daily. However, the efficacy of saquinavir soft gelatin capsules 1200mg once daily plus **atazanavir** 400mg once daily was inferior to that of lopinavir/ **ritonavir** . The favourable effect of **atazanavir** plus **ritonavir** on viral suppression and immunological outcomes was maintained for up to 96 weeks. Tolerability: **Atazanavir** in combination with other antiretroviral drugs was generally well tolerated (treatment duration up to 120 weeks). The type of most treatment-related adverse effects was broadly similar between **atazanavir** recipients and recipients of nelfinavir, **efavirenz** or co-formulated lopinavir/ **ritonavir** , with the exception of jaundice and scleral icterus, which occurred only in patients receiving **atazanavir** . **Atazanavir** -containing regimens were associated with less diarrhoea than nelfinavir- and lopinavir/ **ritonavir** - containing regimens. The most frequent laboratory abnormality associated with the use of **atazanavir** -containing regimens was elevated total bilirubin, predominantly of the unconjugated type, which was generally reversible and not associated with elevated aminotransferase levels. Hyperbilirubinaemia infrequently lead to discontinuation. In addition, the incidence of grade 3 or 4 hyperbilirubinaemia in **atazanavir** recipients was similar between HIV-infected patients positive for hepatitis B and/or C virus and those negative for hepatitis.

DESCRIPTORS:
Atazanavir ; HIV infection; Pharmacodynamics; Pharmacokinetics; Therapeutic use; Tolerability

SPECIES DESCRIPTORS:
Human immunodeficiency virus; Human immunodeficiency virus 1

CLASSIFICATION CODE AND DESCRIPTION:
99 - General

Atazanavir : **A review of its use in the management of HIV infection**
Abstract: **Atazanavir** (Reyataz(R)) is a novel protease inhibitor (PI) approved for use in combination with other...

...HIV infection. In antiretroviral therapy (ART)-experienced patients the drug is administered with low-dose **ritonavir** (i.e. boosted). In the US, unboosted **atazanavir** is also approved for use in ART-naive patients. In adult patients with HIV infection, **atazanavir** -containing highly active

antiretroviral therapy (HAART) regimens provided marked improvements in virological and immunological markers and was generally well tolerated. Furthermore, recommended **atazanavir** regimens were no less effective than, and generally as well tolerated as, other HAART regimens in these patients, including regimens containing co-formulated lopinavir/ **ritonavir** . **Atazanavir** may have an advantage over other PIs because of its favourable effect on lipid profiles...

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...naive patients receiving a dual-nucleoside reverse transcriptase inhibitor (NRTI)-containing regimen, the efficacy of **atazanavir** 400mg once daily was similar to that of nelfinavir 750mg three times daily, nelfinavir 1250mg twice daily or **efavirenz** 600mg once daily after 48 weeks' treatment. Viral suppression was maintained for an additional 24...

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once daily was inferior to that of lopinavir/ **ritonavir** . The favourable effect of **atazanavir** plus **ritonavir** on viral suppression and immunological outcomes was maintained for up to 96 weeks. Tolerability: **Atazanavir** in combination with other antiretroviral drugs was generally well tolerated (treatment duration up to 120 weeks). The type of most treatment-related adverse effects was broadly similar between **atazanavir** recipients and recipients of nelfinavir, **efavirenz** or co-formulated lopinavir/ **ritonavir** , with the exception of jaundice and scleral icterus, which occurred only in patients receiving **atazanavir** . **Atazanavir** -containing regimens were associated with less diarrhoea than nelfinavir- and lopinavir/ **ritonavir** - containing regimens. The most frequent laboratory abnormality associated with the use of **atazanavir** -containing regimens was elevated total bilirubin, predominantly of the unconjugated type, which was generally reversible...

...infrequently lead to discontinuation. In addition, the incidence of grade 3 or 4 hyperbilirubinaemia in **atazanavir** recipients was similar between HIV-infected patients positive for hepatitis B and/or C virus...

DESCRIPTORS:
Atazanavir ; HIV infection; Pharmacodynamics; Pharmacokinetics; Therapeutic use; Tolerability

10/5,K/3 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

15097636 Genuine Article#: 037QK Number of References: 17
Title: Atazanavir **plasma concentrations vary significantly between patients and correlate with increased serum bilirubin concentrations**
Author(s): Smith DE (REPRINT) ; Jeganathan S; Ray J
Corporate Source: Albion St Ctr,150-154 Albion St/Surry Hills/NSW 2010/Australia/ (REPRINT); Albion St Ctr,Sydney/NSW/Australia/; St Vincents Hosp,Sydney/NSW 2010/Australia/(don.smith@sesiahs.health.nsw.gov.au)
Journal: HIV CLINICAL TRIALS, 2006, V7, N1 (JAN-FEB), P34-38
ISSN: 1528-4336 Publication date: 20060100
Publisher: THOMAS LAND PUBLISHERS, INC, 255 JEFFERSON RD, ST LOUIS, MO 63119 USA
Language: English Document Type: ARTICLE
Geographic Location: Australia
Journal Subject Category: INFECTIOUS DISEASES; PHARMACOLOGY & PHARMACY
Abstract: Background: **Atazanavir** (ATV) is recommended to be dosed at 400 mg once daily or 300 mg daily coadministered with 100 mg **ritonavir** (RTV). Method: 31 male patients receiving ATV either alone or boosted with RTV for more than 2 weeks had ATV concentration measured by high performance liquid chromatography (HPLC). ATV concentrations were adjusted to obtain a 24-hour trough level using a standard **pharmacokinetic** formula. Results: 25 samples were taken from patients who received 300 mg ATV, 6 with 200 mg, 3 with 400 mg, and 2 with 150 mg, all boosted with 100 mg RTV. In the unboosted group, patients received 400 mg (7) or 600 mg (2). The median adjusted 24-hour trough ATV concentration was 630 ng/mL (interquartile range [IQR] 355-1034) in the boosted and 113 ng/mL (IQR 50-225) in the unboosted group (p = .001). Median serum bilirubin concentration was 34 IU/L (IQR 27.5-49) and 41 IU/L (IQR 31-45) in the boosted and unboosted groups,

respectively. In the boosted group, high ATV concentrations were significantly correlated with increased serum bilirubin concentrations (p = .003). Conclusion: ATV concentrations showed considerable interpatient variability. Bilirubin concentrations are an indicator of high ATV concentrations and may prove to be useful in selecting patients for therapeutic drug monitoring (TDM).
Descriptors--Author Keywords: **atazanavir ;** bilirubin ; HIV ; therapeutic drug level monitoring ; toxicity
Identifiers--KeyWord Plus(R): ACTIVE ANTIRETROVIRAL THERAPY; LAMIVUDINE; **EFAVIRENZ;** COMBINATION; STAVUDINE; **RITONAVIR;** FAILURE; HIV
Cited References:

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YENI PG, 2004, V292, P251, JAMA-J AM MED ASSOC

Title: Atazanavir **plasma concentrations vary significantly between patients and correlate with increased serum bilirubin concentrations**
Abstract: Background: **Atazanavir** (ATV) is recommended to be dosed at 400 mg once daily or 300 mg daily coadministered with 100 mg **ritonavir** (RTV). Method: 31 male patients receiving ATV either alone or boosted with RTV for more...
...HPLC). ATV concentrations were adjusted to obtain a 24-hour trough level using a standard **pharmacokinetic** formula. Results: 25 samples were taken from patients who received 300 mg ATV, 6 with...
...Identifiers--ACTIVE ANTIRETROVIRAL THERAPY; LAMIVUDINE; **EFAVIRENZ;** COMBINATION; STAVUDINE; **RITONAVIR;** FAILURE; HIV

10/5,K/4 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

13637241 Genuine Article#: 899TR Number of References: 39
Title: A novel once-daily protease inhibitor
Author(s): Piliero PJ (REPRINT)
Corporate Source: Albany Med Coll,Div HIV Med,47 New Scotland Ave/Albany//NY/12208 (REPRINT); Albany Med Coll,Div HIV Med,Albany//NY/12208(pilierp@mail.amc.edu)
Journal: DRUGS OF TODAY, 2004, V40, N11 (NOV), P901-912
ISSN: 0025-7656 Publication date: 20041100
Publisher: PROUS SCIENCE, SA, PO BOX 540, PROVENZA 388, 08025 BARCELONA, SPAIN
Language: English Document Type: REVIEW

Geographic Location: USA
Journal Subject Category: PHARMACOLOGY & PHARMACY
Abstract: Ataza.navir (formerly BMS-232632), an azapeptide protease inhibitor (PI), is a new human immunodeficiency virus (HIV) treatment that has recently received marketing approval from the FDA. It has a **pharmacokinetic** profile that supports once-daily dosing and has demonstrated a unique resistance profile and superior virologic potency compared with other antiretrovirals in vitro. In subjects with HIV, **atazanavir** (400 mg once daily) produced rapid and sustained improvements in viral load and CD4 counts in both antiretroviral-naive as well as previously treated patients when used in combination with dual nucleoside reverse transcriptase inhibitor (NRTI) treatment. In these studies **atazanavir** demonstrated comparable anti-HIV efficacy to nelfinavir (twice or three times daily), **efavirenz** and the combination of **ritonavir** and saquinavir. However, unlike these comparator agents, **atazanavir** did not adversely affect the plasma lipid profile, an advantage that sets it apart from other currently available PIS. **Atazanavir** was inferior to lopinavir/ **ritonavir** in patients who previously failed an initial protease inhibitor containing regimen. Preliminary results in multiple PI-experienced patients indicate comparable efficacy to lopinavir/ **ritonavir** in subjects receiving a boosted regimen of **atazanavir** plus **ritonavir** . In summary, **atazanavir** offers several therapeutic advantages, including a convenient once-daily dosing schedule, neutral lipid effects and a distinct resistance profile. These characteristics may ultimately help improve adherence, reduce the potential risk of long-term cardiovascular events associated with dyslipidemia, and increase the range of therapeutic options available for patients failing other antiretroviral regimens.
Identifiers--KeyWord Plus(R): HIV-INFECTION; BMS-232632; COMBINATION; **ATAZANAVIR;** PANEL
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*DEP HLTH HUM SERV, 2003, GUID US ANT AG HIV 1
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YENI PG, 2002, V288, P222, JAMA-J AM MED ASSOC

...Abstract: virus (HIV) treatment that has recently received marketing approval from the FDA. It has a **pharmacokinetic** profile that supports once-daily dosing and has demonstrated a unique resistance profile and superior virologic potency compared with other antiretrovirals in vitro. In subjects with HIV, **atazanavir** (400 mg once daily) produced rapid and sustained improvements in viral load and CD4 counts...

...when used in combination with dual nucleoside reverse transcriptase inhibitor (NRTI) treatment. In these studies **atazanavir** demonstrated comparable anti-HIV efficacy to nelfinavir (twice or three times daily), **efavirenz** and the combination of **ritonavir** and saquinavir. However, unlike these comparator agents, **atazanavir** did not adversely affect the plasma lipid profile, an advantage that sets it apart from other currently available PIS. **Atazanavir** was inferior to lopinavir/ **ritonavir** in patients who previously failed an initial protease inhibitor containing regimen. Preliminary results in multiple PI-experienced patients indicate comparable efficacy to lopinavir/ **ritonavir** in subjects receiving a boosted regimen of **atazanavir** plus **ritonavir** . In summary, **atazanavir** offers several therapeutic advantages, including a convenient once-daily dosing schedule, neutral lipid effects and...
...Identifiers--HIV-INFECTION; BMS-232632; COMBINATION; **ATAZANAVIR;** PANEL

10/5,K/5 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

13438437 Genuine Article#: 881WA Number of References: 117
Title: Pharmacokinetics of antiretrovirals in pregnant women
Author(s): Mirochnick M (REPRINT) ; Capparelli E
Corporate Source: Boston Univ,Sch Med,91 E Concord St/Boston//MA/02118 (REPRINT); Boston Univ,Sch Med,Boston//MA/02118; Univ Calif San Diego,Sch Med,San Diego//CA/92103; Univ Calif San Diego,Sch Pharm,San Diego//CA/92103; Univ Calif San Diego,Sch Pharmaceut Sci,San Diego//CA/92103(markm@bu.edu)
Journal: CLINICAL PHARMACOKINETICS, 2004, V43, N15, P1071-1087
ISSN: 0312-5963 Publication date: 20040000
Publisher: ADIS INTERNATIONAL LTD, 41 CENTORIAN DR, PRIVATE BAG 65901, MAIRANGI BAY, AUCKLAND 10, NEW ZEALAND
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Abstract: Antiretroviral treatment of HIV-infected pregnant women is widely used to prevent mother-to-child HIV transmission and as primary therapy of maternal HIV infection. The physiological changes associated with pregnancy have a large impact on drug disposition. and changes in antiretroviral pharmacokinetics during pregnancy must be understood for these drugs to be used safely and effectively in pregnant women.

Zidovuine and didanosine, two of the nucleoside reverse transcriptase inhibitors, demonstrate an increase in clearance and decrease in area under the concentration-time curve during pregnancy. The clinical significance of these changes is unknown due to the lack of a clear relationship between plasma concentrations of nucleoside reverse transcriptase inhibitors and clinical effects. **Pharmacokinetic** parameters of lamivudine, stavudine and abacavir are not significantly changed during pregnancy. There are no data describing the effect of pregnancy on the pharmacokinetics of the other nucleoside/nucleotide analogues (zalcitabine, emtricitabine and tenofovir). Pregnancy does not appear to have a significant effect on the pharmacokinetics of the non-nucleoside reverse transcriptase inhibitor nevirapine and there are no data describing the pharmacokinetics of the other non-nucleoside reverse transcriptase inhibitors (**efavirenz** and delavirdine) during pregnancy.

Reduced plasma concentrations during pregnancy have been described for several of the protease inhibitors, including nelfinavir (with administration of 750mg three times daily), indinavir, saquinavir and Kaletra(R) (a co-formulation of lopinavir and **ritonavir**). Plasma concentrations equivalent to those in nonpregnant adults have been reported in pregnant women receiving nelfinavir at doses of 1250mg twice daily, and the addition of **ritonavir** to saquinavir greatly increases saquinavir exposure to therapeutic concentrations in pregnant women. No pregnancy **pharmacokinetic** data are available for the newer protease inhibitors **atazanavir** and fosamprenavir, or with other dual protease inhibitor combinations that include low dose **ritonavir** to boost concentrations of the coadministered protease inhibitor. Further investigations of antiretroviral pharmacology during pregnancy, including protein binding studies, are urgently needed.

Identifiers--KeyWord Plus(R): HUMAN-IMMUNODEFICIENCY-VIRUS; PERINATAL HIV-1 TRANSMISSION; MATERNAL-FETAL TRANSFER; TO-CHILD TRANSMISSION; PROTEIN-BINDING; HUMAN-PLACENTA; TRANSPLACENTAL PHARMACOKINETICS; ZIDOVUDINE PHOSPHORYLATION; DOSE PHARMACOKINETICS; CELLULAR PHARMACOLOGY

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...Abstract: of a clear relationship between plasma concentrations of nucleoside reverse transcriptase inhibitors and clinical effects. **Pharmacokinetic** parameters of lamivudine, stavudine and abacavir are not significantly changed during pregnancy. There are no...

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Reduced plasma concentrations during pregnancy have been described for several of...

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10/5,K/6 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

13315234 Genuine Article#: 868IS Number of References: 61
Title: Practical guidelines to interpret plasma concentrations of antiretroviral drugs
Author(s): Kappelhoff BS (REPRINT) ; Crommentuyn KML; de Maat MMR; Mulder JW; Huitema ADR; Beijnen JH
Corporate Source: Slotervaart Hosp,Dept Pharm & Pharmacol,Louwesweg 6/NL-1066 EC Amsterdam//Netherlands/ (REPRINT); Slotervaart Hosp,Dept Pharm & Pharmacol,NL-1066 EC Amsterdam//Netherlands/; Slotervaart Hosp,Dept Internal Med,Amsterdam//Netherlands/; Univ Utrecht,Fac Pharmaceut Sci, Div Drug Toxicol, Dept Biomed Anal,Utrecht//Netherlands/(Apbkp@slz.nl)
Journal: CLINICAL PHARMACOKINETICS, 2004, V43, N13, P845-853
ISSN: 0312-5963 Publication date: 20040000
Publisher: ADIS INTERNATIONAL LTD, 41 CENTORIAN DR, PRIVATE BAG 65901, MAIRANGI BAY, AUCKLAND 10, NEW ZEALAND
Language: English Document Type: REVIEW
Geographic Location: Netherlands
Journal Subject Category: PHARMACOLOGY & PHARMACY
Abstract: Several relationships have been reported between antiretroviral drug concentrations and the efficacy of treatment, and toxicity. Therefore, therapeutic drug monitoring (TDM) may be a valuable tool in improving the treatment of HIV-1-infected patients in daily practice. In this regard, several measures of exposure have been studied, e.g. trough and maximum concentrations, concentration ratios and the inhibitory quotient. However, it has not been unambiguously established which **pharmacokinetic** parameter should be monitored to maintain optimal viral suppression. Each **pharmacokinetic** parameter has its pros and cons. Many factors can affect the pharmacokinetics of antiretroviral agents, resulting in variability in plasma concentrations between and within patients. Therefore, plasma concentrations should be considered on several occasions. In addition, the interpretation of the drug concentration of a patient should be performed on an individual basis, taking intoaccount the clinical condition of the patient. Important factors herewith are viral load, immunology, occurrence of adverse events, resistance pattern and comedication.

In spite of the described constraints, the aim of this review is to provide a practical guide for TDM of antiretroviral agents. This,

article outlines pharmaco-kinetic target values for the HIV protease inhibitors amprenavir **atazanavir** , indinavir,lopinavir, nelfinavir, **ritonavir** and saquinavir, and the non-nucleoside, reverse transcriptase inhibitors **efavirenz** and nevirapine. Detailed advice is provided on how-to interpret the results of TDM of these drugs.

Identifiers--KeyWord Plus(R): HIV-INFECTED PATIENTS; CONTAINING TRIPLE THERAPY; HIV-1-INFECTED INDIVIDUALS; TREATMENT FAILURE; VIROLOGICAL RESPONSE; POSITIVE PATIENTS; SALVAGE THERAPY; INDINAVIR; **RITONAVIR**; NELFINAVIR

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YENI PG, 2002, V288, P222, JAMA-J AM MED ASSOC

...Abstract: concentrations, concentration ratios and the inhibitory quotient. However, it has not been unambiguously established which **pharmacokinetic** parameter should be monitored to maintain optimal viral suppression. Each **pharmacokinetic** parameter has its pros and cons. Many factors can affect the pharmacokinetics of antiretroviral agents...

...antiretroviral agents. This, article outlines pharmaco-kinetic target values for the HIV protease inhibitors amprenavir **atazanavir** , indinavir,lopinavir, nelfinavir, **ritonavir** and saquinavir, and the non-nucleoside, reverse transcriptase inhibitors **efavirenz** and nevirapine. Detailed advice is provided on how-to interpret the results of TDM of...
...Identifiers--TRIPLE THERAPY; HIV-1-INFECTED INDIVIDUALS; TREATMENT FAILURE; VIROLOGICAL RESPONSE; POSITIVE PATIENTS; SALVAGE THERAPY; INDINAVIR; **RITONAVIR;** NELFINAVIR

10/5,K/7 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

12923783 Genuine Article#: 835EK Number of References: 39
Title: Atazanavir : **A new protease inhibitor to treat HIV infection**
Author(s): Musial BL (REPRINT) ; Chojnacki JK; Coleman CI
Corporate Source: Univ Connecticut,Hartford Hosp, Drug Informat Ctr, Sch Pharm,80 Seymour St/Hartford//CT/06102 (REPRINT); Univ Connecticut,Hartford Hosp, Drug Informat Ctr, Sch Pharm,Hartford//CT/06102; Connecticut Vet Adm Healthcare Syst,West Haven//CT/(ccolema@harthosp.org)
Journal: AMERICAN JOURNAL OF HEALTH-SYSTEM PHARMACY, 2004, V61, N13 (JUL 1) , P1365-1374
ISSN: 1079-2082 Publication date: 20040701
Publisher: AMER SOC HEALTH-SYSTEM PHARMACISTS, 7272 WISCONSIN AVE, BETHESDA, MD 20814 USA
Language: English Document Type: ARTICLE
Geographic Location: USA
Journal Subject Category: PHARMACOLOGY & PHARMACY
Abstract: Purpose. The pharmacology, pharmacokinetics, and clinical trials of and drug interactions and formulary considerations associated with **atazanavir** , the newest protease inhibitor (PI) to treat human immunodeficiency virus (HIV) infection, are evaluated.

Summary. Clinical and **pharmacokinetic** trials were identified through a MEDLINE search. In addition, all available literature citations and meeting abstracts were obtained from the drug's manufacturer. All articles identified from the data sources were evaluated, and all information deemed relevant was included in this review. Data on **atazanavir** for the treatment of HIV infection are limited to several phase II and III trials, one of which is still ongoing. **Atazanavir** has shown efficacy comparable with other Pis and the nonnucleoside reverse-transcriptase inhibitor **efavirenz** in reducing HIV RNA levels, increasing CD4+ lymphocyte counts, and increasing the percentage of patients achieving clinically undetectable HIV RNA levels when given as the sole PI in treatment-naive patients, in combination with saquinavir in treatment-experienced patients, and with **ritonavir** -boosting regimens in highly treatment-experienced patients. Treatment-naive patients receiving **atazanavir** commonly develop a protease enzyme mutation on codon 50, which decreases HIV's susceptibility to **atazanavir** but may increase the susceptibility of the virus to other Pis. When **atazanavir** is given to patients with preexisting PI-related mutations, the virus's susceptibility to **atazanavir** is greatly reduced. The occurrence of lipid abnormalities, which has been a major concern with previous Pis, has not been shown to be troublesome in patients receiving **atazanavir** .

Conclusion. **Atazanavir** may be used alone as a first-line PI, with saquinavir in treatment-experienced patients, or in combination with a **ritonavir** -boosting regimen in highly treatment-experienced patients as part of a salvage regimen.

Descriptors--Author Keywords: antiretroviral agents ; **atazanavir** ; combined therapy ; drug interactions ; formularies ; HIV infections ; mechanism of action ; pharmacokinetics ; resistance ; **ritonavir** ; saquinavir ; toxicity

Identifiers--KeyWord Plus(R): HUMAN-IMMUNODEFICIENCY-VIRUS; ANTIRETROVIRAL THERAPY; CLINICAL-TRIAL; COMBINATION; BMS-232632; MANAGEMENT; ADULTS; PANEL

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Title: Atazanavir : **A new protease inhibitor to treat HIV infection**

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Summary. Clinical and **pharmacokinetic** trials were identified through a MEDLINE search. In addition, all available literature citations and meeting...

...sources were evaluated, and all information deemed relevant was included in this review. Data on **atazanavir** for the treatment of HIV infection are limited to several phase II and III trials, one of which is still ongoing. **Atazanavir** has shown efficacy comparable with other Pis and the nonnucleoside reverse-transcriptase inhibitor **efavirenz** in reducing HIV RNA levels, increasing CD4+ lymphocyte counts, and increasing the percentage of patients...

...PI in treatment-naive patients, in combination with saquinavir in treatment-experienced patients, and with **ritonavir** -boosting regimens in highly treatment-experienced patients. Treatment-naive patients receiving **atazanavir** commonly develop a protease enzyme mutation on codon 50, which decreases HIV's susceptibility to **atazanavir** but may increase the susceptibility of the virus to other Pis. When **atazanavir** is given to patients with preexisting PI-related mutations, the virus's susceptibility to **atazanavir** is greatly reduced. The occurrence of lipid abnormalities, which has been a major concern with previous Pis, has not been shown to be troublesome in patients receiving **atazanavir** .

Conclusion. **Atazanavir** may be used alone as a first-line PI, with saquinavir in treatment-experienced patients, or in combination with a **ritonavir** -boosting regimen in highly treatment-experienced patients as part of a salvage regimen.

10/5,K/8 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

15234708 PMID: 15645003

Atazanavir : **A novel once-daily protease inhibitor.**

Piliero Peter J

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Publishing Model Print

Document type: Journal Article; Review

Languages: ENGLISH

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Subfile: INDEX MEDICUS

Atazanavir (formerly BMS-232632), an azapeptide protease inhibitor (PI), is a new human immunodeficiency virus (HIV) treatment that has recently received marketing approval from the FDA. It has a **pharmacokinetic** profile that supports once-daily dosing and has demonstrated a unique resistance profile and superior virologic potency compared with other antiretrovirals in vitro. In subjects with HIV, **atazanavir** (400 mg once daily) produced rapid and sustained improvements in viral load and CD4 counts in both antiretroviral-naive as well as previously treated patients when used in combination with dual nucleoside reverse transcriptase inhibitor (NRTI) treatment. In these studies **atazanavir** demonstrated comparable anti-HIV efficacy to nelfinavir (twice or three times daily), **efavirenz** and the combination of **ritonavir** and saquinavir. However, unlike these comparator agents, **atazanavir** did not adversely affect the plasma lipid profile, an advantage that sets it apart from other currently available PIs. **Atazanavir** was inferior to lopinavir/ **ritonavir** in patients who previously failed an initial protease inhibitor containing regimen. Preliminary results in multiple PI-experienced patients indicate comparable efficacy to lopinavir/ **ritonavir** in subjects receiving a boosted regimen of **atazanavir** plus **ritonavir** . In summary, **atazanavir** offers several therapeutic advantages, including a convenient once-daily dosing schedule, neutral lipid effects and a distinct resistance profile. These characteristics may ultimately help improve adherence, reduce the potential risk of long-term cardiovascular events associated with dyslipidemia, and increase the range of therapeutic options available for patients failing other antiretroviral regimens. (41 Refs.)

Tags: Male

Descriptors: *HIV Infections--drug therapy--DT; *HIV Protease Inhibitors; *Oligopeptides; *Pyridines; Area Under Curve; Biological Availability; Drug Therapy, Combination; HIV Protease Inhibitors--metabolism--ME; HIV Protease Inhibitors--pharmacokinetics--PK; HIV Protease Inhibitors --pharmacology--PD; Half-Life; Humans; Intestinal Absorption; Oligopeptides --metabolism--ME; Oligopeptides--pharmacokinetics--PK; Oligopeptides --pharmacology--PD; Pyridines--metabolism--ME; Pyridines--pharmacokinetics --PK; Pyridines--pharmacology--PD; Randomized Controlled Trials

CAS Registry No.: 0 (HIV Protease Inhibitors); 0 (Oligopeptides); 0 (Pyridines); 198904-31-3 (atazanavir)

Record Date Created: 20050112

Record Date Completed: 20050405

Atazanavir : **A novel once-daily protease inhibitor.**

Atazanavir (formerly BMS-232632), an azapeptide protease inhibitor (PI), is a new human immunodeficiency virus (HIV) treatment that has recently received marketing approval from the FDA. It has a **pharmacokinetic** profile that supports once-daily dosing and has

demonstrated a unique resistance profile and superior virologic potency compared with other antiretrovirals in vitro. In subjects with HIV, **atazanavir** (400 mg once daily) produced rapid and sustained improvements in viral load and CD4 counts...

... when used in combination with dual nucleoside reverse transcriptase inhibitor (NRTI) treatment. In these studies **atazanavir** demonstrated comparable anti-HIV efficacy to nelfinavir (twice or three times daily), **efavirenz** and the combination of **ritonavir** and saquinavir. However, unlike these comparator agents, **atazanavir** did not adversely affect the plasma lipid profile, an advantage that sets it apart from other currently available PIs. **Atazanavir** was inferior to lopinavir/ **ritonavir** in patients who previously failed an initial protease inhibitor containing regimen. Preliminary results in multiple PI-experienced patients indicate comparable efficacy to lopinavir/ **ritonavir** in subjects receiving a boosted regimen of **atazanavir** plus **ritonavir** . In summary, **atazanavir** offers several therapeutic advantages, including a convenient once-daily dosing schedule, neutral lipid effects and...
Chemical Name: HIV Protease Inhibitors; Oligopeptides; Pyridines; **atazanavir**

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S6           0   RITONAVIR AND AFAZANAVIR
S7         369   RITONAVIR AND ATAZANAVIR
S8         119   S5 AND S7
S9          13   S8 AND PHARMACOKINETIC
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16/5,K/1 (Item 1 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE

01311641 1999052207
Drug interactions of HIV protease inhibitors
Malaty L.I.; Kuper J.J.
ADDRESS: Dr. J.J. Kuper, Department of Pharmacy, R. Wood Johnson University Hospital, New Brunswick, NJ 08903, United States
EMAIL: jkuper@rci.rutgers.edu
Journal: Drug Safety, 20/2 (147-169), **1999** , New Zealand
CODEN: DRSAE
ISSN: 0114-5916
DOCUMENT TYPE: Review
LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 93

All the currently available protease inhibitors are metabolised by the **cytochrome** P450 (**CYP**) enzyme system. All are inhibitors of CYP3A4, ranging from weak inhibition for saquinavir to very potent inhibition for **ritonavir** . Thus, they are predicted to have numerous drug interactions, although few such interactions have actually been documented either in **pharmacokinetic** studies or in clinical reports. This article reviews the published literature with an emphasis on the magnitude of interactions and on practical recommendations for management. Many of the drugs commonly taken by patients with HIV have a strong potential to interact with the protease inhibitors. In particular, the non-nucleoside reverse transcriptase inhibitors are also metabolised by **CYP** and have been shown to interact with protease inhibitors. Delaviridine is an inhibitor of CYP3A4, but nevirapine and **efavirenz** are inducers of CYP3A4. The protease inhibitors also interact with each other, and these interactions are being explored for their potential therapeutic benefits. Other commonly used drugs are also known to affect protease inhibitor metabolism, including inhibitors such as clarithromycin and the azole antifungals and inducers such as the rifamycins. Drugs that are known to be significantly affected by the protease inhibitors include ethinylestradiol and terfenadine; many other drugs have lesser or potential interactions. Although little specific data is available on the drug interactions of protease inhibitors, this lack of data should not be interpreted as a lack of interaction. Retrospective chart reviews have demonstrated that potentially severe drug interactions are frequently overlooked. Much more clinical data is needed, but pharmacists and physicians must always be vigilant for drug interactions, both those that are already documented and those that are predictable from **pharmacokinetic** profiles, in patients receiving protease inhibitors.

CLASSIFICATION CODE AND DESCRIPTION:
86.7.7.9 - IMMUNOLOGY AND INFECTIOUS DISEASES / IMMUNITY TO INFECTION / AIDS and HIV / Molecular biology of HIV

, **1999**

All the currently available protease inhibitors are metabolised by the **cytochrome** P450 (**CYP**) enzyme system. All are inhibitors of CYP3A4,

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...the protease inhibitors. In particular, the non-nucleoside reverse transcriptase inhibitors are also metabolised by **CYP** and have been shown to interact with protease inhibitors. Delaviridine is an inhibitor of CYP3A4, but nevirapine and **efavirenz** are inducers of CYP3A4. The protease inhibitors also interact with each other, and these interactions...

...for drug interactions, both those that are already documented and those that are predictable from **pharmacokinetic** profiles, in patients receiving protease inhibitors.

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  File 155:MEDLINE(R) 1950-2006/Jul 31
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 4/5,K/1     (Item 1 from file: 34)
DIALOG(R)File  34:SciSearch(R) Cited Ref Sci
(c) 2006 The Thomson Corp. All rts. reserv.

09518086   Genuine Article#: 415BP   Number of References: 86
Title: Saquinavir soft gelatin capsule - A comparative safety review
Author(s): Gill J (REPRINT) ; Feinberg J
Corporate Source: Foothills Hosp,So Alberta HIV Clin,213 906-8 Ave
    SW/Calgary/AB T2P 1H9/Canada/ (REPRINT); Foothills Hosp,So Alberta HIV
    Clin,Calgary/AB T2P 1H9/Canada/; Univ Cincinnati,Med Ctr, Ctr Infect
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Dis,Cincinnati//OH/45267
Journal: DRUG SAFETY, **2001** , V24, N3, P223-232
ISSN: 0114-5916 Publication date: 20010000
Publisher: ADIS INTERNATIONAL LTD, 41 CENTORIAN DR, PRIVATE BAG 65901, MAIRANGI BAY, AUCKLAND 10, NEW ZEALAND
Language: English Document Type: REVIEW
Geographic Location: Canada; USA
Journal Subject Category: PUBLIC, ENVIRONMENTAL & OCCUPATIONAL HEALTH; PHARMACOLOGY & PHARMACY; TOXICOLOGY
Abstract: The HIV-1 protease inhibitor (PI) saquinavir is available as a soft gelatin capsule (SGC) formulation. At the recommended dosage of saquinavir SGC (1200mg 3 times daily), this formulation provides around 8-fold greater exposure than the established hard gelatin capsule (HGC) formulation at the recommended dosage of 600mg 3 times daily.

As with the HGC formulation, the most common adverse events seen with saquinavir SGC are gastrointestinal symptoms (e.g. diarrhoea, abdominal discomfort and nausea). Some of these may occur with a slightly higher frequency with the SGC than with the HGC formulation. Saquinavir SGC has only a minimal effect on nonfasting serum lipid and cholesterol levels.

Like other PIs, saquinavir is metabolised by the **cytochrome** P450 (**CYP**) 3A4 isoenzyme and is susceptible to interactions with inducers (e.g. rifabutin and rifampicin) and inhibitors (e.g. clarithromycin and ketoconazole) of this enzyme. **Ritonavir** , nelfinavir, indinavir and delavirdine, all CYP3A4 inhibitors, greatly increase saquinavir plasma concentrations and the therapeutic implications of these interactions continue to he evaluated. While saquinavir is the least potent **CYP** 3A inhibitor among the PIs, several drugs (notably terfenadine, astemizole and cisapride) should not be given in combination with saquinavir.

Therefore, although the SGC formulation enhances saquinavir exposure, it has a similar safety profile to the HGC formulation.

Saquinavir, formulated as the hard gelatin capsule (HGC) formulation. was the first HIV protease inhibitor (PI) to be approved for the treatment of HIV infection. When used in combination with other antiretrovirals, saquinavir HGC has been demonstrated to provide a survival advantage,([1-4]) although the poor bioavailability of this formulation means that it is less effective than the other currently licensed PIs. Subsequently, saquinavir has been reformulated as an enhanced soft gelatin capsule (SGC), resulting in increased drug exposure and enhanced antiretroviral activity compared with the HGC formulation.([5,6]) The currently recommended dosage of saquinavir SGC, 1200mg 3 times daily, provides around 8-fold greater exposure than the recommended dosage of the HGC formulation (600mg 3 times daily), as quantified by the area under the curve to 24 hours(**AUC** (0-24h)).([6])

This review focuses on the safety profile of saquinavir SGC and compares it with the safety profiles of other PIs. Pertinent data concerning the **non - nucleoside reverse transcriptase** inhibitors (NNRTIs) delavirdine, nevirapine and efavirenz, and the reverse transcriptase inhibitors (NRTIs), including abacavir, are also considered. The review incorporates data from published literature sources (e.g. MEDLINE), case reports, conference abstracts and prescribing information. Information was selected on the basis of relevancy to the subject and the most pertinent and recent data was

cited as far as practicable.
Identifiers--KeyWord Plus(R): IMMUNODEFICIENCY-VIRUS PROTEASE; HUMAN LIVER-MICROSOMES; HIV-INFECTION; ANTIRETROVIRAL THERAPY; METABOLIC ABNORMALITIES; DRUG-INTERACTIONS; BUFFALO HUMP; INHIBITORS; **RITONAVIR**; INDINAVIR
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VONMOLTKE LL, 1998, V38, P106, J CLIN PHARMACOL
WOOLLEY J, 1997, 37 INT C ANT AG CHEM
YUEN GJ, 1997, 98 ANN M AM SOC CLIN

, **2001**

...Abstract: on nonfasting serum lipid and cholesterol levels.

Like other PIs, saquinavir is metabolised by the **cytochrome** P450 (**CYP**) 3A4 isoenzyme and is susceptible to interactions with inducers (e.g. rifabutin and rifampicin) and inhibitors (e.g. clarithromycin and ketoconazole) of this enzyme. **Ritonavir** , nelfinavir, indinavir and delavirdine, all CYP3A4 inhibitors, greatly increase saquinavir plasma concentrations and the therapeutic implications of these interactions continue to he evaluated. While saquinavir is the least potent **CYP** 3A inhibitor among the PIs, several drugs (notably terfenadine, astemizole and cisapride) should not be...

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...Identifiers--PROTEASE; HUMAN LIVER-MICROSOMES; HIV-INFECTION;
ANTIRETROVIRAL THERAPY; METABOLIC ABNORMALITIES; DRUG-INTERACTIONS;
BUFFALO HUMP; INHIBITORS; **RITONAVIR;** INDINAVIR

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  $38.24  Estimated total session cost   3.286 DialUnits


Logoff: level 05.12.03 D  17:36:40


You are now logged off
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